



Published in final edited form as:

J Theor Comput Chem. 2013 December ; 12(8): . doi:10.1142/S021963361341006X.

Multiscale Multiphysics and Multidomain Models I: Basic Theory

Guo-Wei Wei*

Department of Mathematics Michigan State University, MI 48824, USA Department of Electrical and Computer Engineering Michigan State University, MI 48824, USA Department of Biochemistry and Molecular Biology Michigan State University, MI 48824, USA

Abstract

This work extends our earlier two-domain formulation of a differential geometry based multiscale paradigm into a multidomain theory, which endows us the ability to simultaneously accommodate multiphysical descriptions of aqueous chemical, physical and biological systems, such as fuel cells, solar cells, nanofluidics, ion channels, viruses, RNA polymerases, molecular motors and large macromolecular complexes. The essential idea is to make use of the differential geometry theory of surfaces as a natural means to geometrically separate the macroscopic domain of solvent from the microscopic domain of solute, and dynamically couple continuum and discrete descriptions. Our main strategy is to construct energy functionals to put on an equal footing of multiphysics, including polar (i.e., electrostatic) solvation, nonpolar solvation, chemical potential, quantum mechanics, fluid mechanics, molecular mechanics, coarse grained dynamics and elastic dynamics. The variational principle is applied to the energy functionals to derive desirable governing equations, such as multidomain Laplace-Beltrami (LB) equations for macromolecular morphologies, multidomain Poisson-Boltzmann (PB) equation or Poisson equation for electrostatic potential, generalized Nernst-Planck (NP) equations for the dynamics of charged solvent species, generalized Navier-Stokes (NS) equation for fluid dynamics, generalized Newton's equations for molecular dynamics (MD) or coarse-grained dynamics and equation of motion for elastic dynamics. Unlike the classical PB equation, our PB equation is an integral-differential equation due to solvent-solute interactions. To illustrate the proposed formalism, we have explicitly constructed three models, a multidomain solvation model, a multidomain charge transport model and a multidomain chemo-electro-fluid-MD-elastic model. Each solute domain is equipped with distinct surface tension, pressure, dielectric function, and charge density distribution. In addition to long-range Coulombic interactions, various non-electrostatic solvent-solute interactions are considered in the present modeling. We demonstrate the consistency between the non-equilibrium charge transport model and the equilibrium solvation model by showing the systematical reduction of the former to the latter at equilibrium. This paper also offers a brief review of the field.

Keywords

Multiscale; Multiphysics; Multidomain; Laplace-Beltrami equation; Poisson-Boltzmann equation; Nernst-Planck equation; Fluid dynamics; Molecular dynamics; Elastic dynamics

* Address correspondences to Guo-Wei Wei. wei@math.msu.edu.

I Introduction

An important trend in contemporary life sciences is that with the availability of modern biotechnologies, traditional disciplines, such as physiology, plant biology, neuroscience etc, are undergoing a fundamental transition from macroscopic phenomenological ones into molecular based biosciences. In parallel with this development, a major feature of life sciences in the 21st Century is their transformation from phenomenological and descriptive disciplines to quantitative and predictive ones. Ample opportunities have emerged for mathematically driven advances in biological research. Experimental exploration of self-organizing molecular biological systems, such as HIV viruses, molecular motors, ribosomes, RNA polymerase and proteins in Alzheimer's disease, are examples of dominating driving forces in scientific discovery and innovation in the past few decades. However, the emergence of excessive complexity in self-organizing biological systems poses fundamental challenges to their quantitative description, because of their excessively high dimensionality and the complexity of processes involved. Mathematical approaches that are able to efficiently reduce the number of degrees of freedom, and model complex biological systems, are becoming increasingly popular in molecular biosciences. Multiscale modeling, intrinsic manifold extraction, dimensionality reduction and machine learning techniques are introduced to reduce the complexity of biomolecular systems while maintaining an essential and adequate description of the biomolecular observables of interest.

Recently, multiscale and multiphysics modeling and computation have become some of the most powerful approaches in chemistry, physics, biology, nanoscience and engineering.^{1,29,56,95,146,148,162,164,166,180} Most of these approaches are aimed at the understanding of complex systems, such as complex fluids, turbulent flows, microfluidics,^{29,180} soft material, solids, interface problems, structure and fluid interactions, wave propagation in random media, stochastic processes, deoxyribonucleic acid (DNA) nanowires, molecular junctions, solar cells, fuel cells, battery cells, molecular switches, nanotubes, field effect transistors, nanofibers, thin films, ion channels, ATPases, neuron synapses, and self-similar problems. A main purpose of developing multiscale models is to maintain efficient descriptions of key physical measurements in multiphysical problems while avoid detailed descriptions of some physical components that do not significantly contribute to the behavior of physical observations of interest, so that the resulting computations are feasible with the current computer capability. In the past two decades, a large variety of multiscale models and algorithms has been proposed. Among them, many multiscale models, such as Boltzmann theory kinetic theory,^{141-143,158} describe multiphysics with multiple governing equations, such as microscopic laws for atoms and molecules at microscopic settings, and transport equations for the conservation of mass, momentum, and energy at macroscopic settings. Multiscale approaches that bridge macro-micro scales and couple macro-micro domains are commonly used.¹⁴⁸ An interesting class of multiscale models has their origin from earlier wavelet multiresolution analysis. Yet the other class of multiscale approaches is heterogeneous multiscale models.⁵⁶ Multiscale coarse-grained methods¹⁰² and quantum mechanical/molecular mechanical (QM/MM) approaches^{46,65,77,78} are developed for bimolecular systems. Multigrid methods which extract and utilize information at different time or spatial scales governed by one or a few

equations can also be regarded as multiscale approaches. An elegant example is the homogenization method.

A new class of multiscale models, differential geometry based multiscale approaches, has been introduced by the present author¹⁶⁴ for large chemical, physical and biological systems and nano devices, such as fuel cells, solar cells, nanofluidics, ion channels, molecular motors, subcellular organelles, and virus complexes. A common feature in these systems is that they have aqueous environment. We seek multiscale models which provide microscopic descriptions of chemical and biological subjects of interest, while maintain macroscopic descriptions of the aqueous environment, so as to significantly reduce the number of degrees of freedom of the original complex system. To this end, we make use of the differential geometry theory of surfaces and the geometric measure theory as a natural means to separate macroscopic and microscopic domains.^{8-10,163,165} A variational strategy developed in our earlier work for the minimal molecular surfaces^{9,10} is generalized to cast our multiscale modeling of multiphysics in a self-consistent manner. Our differential geometry based multiscale paradigm provides variational formulations to a number of physical phenomena, including polar and nonpolar solvations, molecular dynamics, fluid dynamics, electrokinetics, electrohydrodynamics, electrophoresis, and elastic dynamics. By using the Euler-Lagrange variation, coupled Laplace-Beltrami equation and Poisson-Boltzmann equation are obtained for solvation. For non-equilibrium systems, additional generalized Poisson-Nernst-Planck equations and/or Navier-Stokes equations are derived for the charged species. Multiscale Newton's equations are obtained to allow the molecular mechanics (MM) description of biomolecular systems. Finally, for excessively large chemical and biological systems, the linear elastic dynamics is employed to replace expensive MD simulations and further reduce the dimensionality.

Differential geometry based multiscale models have been intensively validated in the past three years.^{21,23,31-34,166} The first series of efforts was given to the multiscale solvation analysis.^{31-34,79,149,179} We implement differential geometry based solvation models in both the Eulerian formulation³¹ and the Lagrangian formulation³² for real-world problems. We analyze the equivalence of these formulations for both small and large molecules. An immediate consequence of this development is a significant reduction in the number of free parameters that users must "fit" or adjust in applications to real-world systems. The surfaces generated by our methods are free of geometric singularities, which commonly occur in conventional molecular surfaces and cause computational instabilities.^{43,132} Very good consistency between our theoretical predictions and experimental solvation energies has been found for tens of compounds.^{31,32} The robustness of the approach was confirmed.^{149,176} Our differential geometry based nonpolar model gives rise to some of the best predictions of nonpolar solvation energies.³⁴ To further improve the accuracy of our multiscale models, we have introduced the quantum density functional theory (DFT) description of solute molecules,³³ which significantly improves the predictive power of our earlier solvation models. In a series of parallel efforts, we have developed differential geometry based multi-scale quantum models for proton transport.^{21,23} Proton transport underpins the molecular mechanism in biological energy transduction, sensory systems and reproduction of influenza A viruses.²⁷ Due to significant quantum effects, proton permeation across membrane proteins needs to be treated by quantum mechanical

means.^{116,125} In our multiscale and multiphysics model, we have constructed a new density functional theory based on the Boltzmann statistics, rather than the Fermi-Dirac statistics, to describe proton dynamics quantum mechanically, while implicitly treat numerous solvent molecules as a dielectric continuum. The membrane proteins are described in the atomistic detail to enable the gating effect. An interesting aspect is that the densities of all the other ions in the solvent are treated with the Boltzmann distributions following an approach introduced in our earlier work,¹⁷⁸ which was independently confirmed by using Monte Carlo simulations.⁹⁴ We have explored non-electrostatic van der Waals interactions among all the ions, and between ions and proteins, including size (steric) effects.²³ Our method provides excellent predictions of experimental current-voltage curves. Most recently, we have developed differential geometry based multiscale models for heterogeneous chemical and biological systems that are far from equilibrium.¹⁶⁶ In this new theory, the consistency between the equilibrium model and the non-equilibrium is established at equilibrium as demonstrated both theoretically and numerically. Our main focus in such a development lies in the understanding of ion channel gating mechanism in membrane proteins. With our variational multiscale framework, we consider both nonpolar and polar (electrostatic) solvation effects, chemical potential and the associated free energy, continuous modeling of solvent species and discrete representation of membrane proteins. Once again, we found very good agreements between our model predictions and experimental measurements.¹⁶⁶

The objective of the present work is to extend our earlier differential geometry based multiscale and multiphysics models into multiscale, multiphysics and multidomain models. Indeed, in our previous formulations, only one solute domain is considered, although it can be described either by using a set of discrete point charges, molecular dynamics, quantum mechanics or with elastic dynamics. In this work, we consider arbitrarily many solute domains so as to allow simultaneously multiphysical descriptions for different macromolecular domains and complex nano-bio devices. For example, in solvation analysis, our multidomain models assign different part of macromolecular complexes with different dielectric functions.^{28,127} This approach is potentially useful to the theoretical analysis of metalloproteins, which are crucial to many cellular different functions in cells, such as signal transduction, oxygen carrier (hemoglobin), and electron transfer (cytochrome). Approximately half of all proteins are metalloproteins. Another example is that in ion channel analysis, we can model the ion channel protein by molecular mechanics while describe the bending and vibration of membrane bilayers with elastic dynamics. Figure 1 illustrates a membrane protein complex, in which the transmembrane protein can be described by molecular mechanics or quantum mechanics, while the solvent can be treated by fluid mechanics. The lipid bilayer can be represented by elastic theory. In fact, hydrophilic head groups in the lipid bilayer can have dielectric functions different from those of hydrophobic tails. Other distinct chemistry or biology in the complex can be described by necessary means as well. Finally, for multidomain or multi-subunit proteins, different domains or subunits can be treated with different approaches, depending on physical observables and practical needs.

The rest of this paper is organized as follows. Section II is devoted to the theory and formulation of our new models. We first describe the notation and scope of the present work. The interaction potentials for different physical laws, including global Coulombic

interactions, solvent-solute interactions and interactions between different solvent species, are considered. Based on this preparation, we introduce three new multiscale, multiphysics and multidomain models. Our first model is for solvation analysis. We introduce a multidomain representation of macromolecular complexes, in which each domain has its own surface tension, pressure, dielectric function, and charge density distribution. The energy variation leads to a set of Laplace-Beltrami equations, each for one solute domain. A generalized Poisson-Boltzmann equation is also derived from the present formulation. We expect this model to provide an efficient description for ion microstructures near the interface. Our second model is for charge transport in chemical, physical and biological systems. This model is a natural extension of the multiscale, multiphysics and multidomain solvation model. The chemical energy functional is employed to allow the description of non-equilibrium charge transport. The standard gradient flow procedure is employed to construct the generalized Nernst-Planck equation. A set of coupled Laplace-Beltrami, Poisson-Nernst-Planck equations are obtained from the variational analysis. This model is relevant to ion channel, nanofluidic and fuel cell systems. Finally, we construct a chemo-electro-fluid-MD-elastic model. This model allows simultaneously three different treatments, discrete point charges, molecular mechanics and elastic dynamics, of charge transfer macromolecular complexes, fuel cells and solar cells. In the solvent domain, multiple solvent species and their fluid flows are considered. This paper ends with concluding remarks.

II Variational multiscale multiphysics and multidomain models

In this section, we discuss a family of variational multiscale multiphysics and multidomain models. Our formulation extends the theory of the differential geometry based multiscale models¹⁶⁴ with the multidomain consideration. The novelty of our new models is the use of multiple domains to accommodate multiphysics descriptions of large biomolecular complexes and nano-bio systems.

We first discuss the scope of the present multiscale multiphysics and multidomain modeling. Three different models, a solvent model, a charge transport model, and a chemo-electro-fluid-MD-elastic model, are developed to illustrate our ideas.

II.A Scope of the present formulation

We denote $\Omega \subset \mathbb{R}^3$ as the total domain. Assume that there are a total of N macromolecular domains, denoted as, $\Omega_I, I = 1, 2, \dots, N$. We characterize these domains by a set of hypersurface functions $\{S_I\}, I = 1, 2, \dots, N$, such as $\mathbf{r} \in \Omega_I$, if $S_I(\mathbf{r}) > 0$. Obviously, these domains overlap each other, $\cap_I \Omega_I > 0$. Additionally, we denote $S_s = 1 - S = 1 - \sum_{I=1}^N S_I$ the solvent characteristic function. The solvent domain is labeled as Ω_s . Obviously, the sum of all characteristic functions is the partition of unity $\sum_{I=1}^N S_I + S_s = 1$.

Electrostatic interactions are fundamental in nature and ubiquitous in all biomolecules, including proteins, nucleic acids, lipid bilayers, sugars, etc. Electrostatic interactions are inherently of long range, which leads to computational difficulties. Since 65-90 percent of cellular mass is water under physiological condition, biomolecules live in a heterogeneous

environment, where they interact with a wide range of aqueous ions, counterions, and other molecules. As a result, electrostatic interactions often manifest themselves in a vast variety of different forms, due to polarization, hyperpolarization, vibrational and rotational averages, screening effects, etc, to mention just a few. The importance of electrostatics in biomolecular systems and nano devices cannot be overemphasized because they underpin the molecular mechanism for almost all important biological processes, including signal transduction, DNA recognition, transcription, post-translational modification, translation, protein folding and protein ligand binding. In general, electrostatics is often the fundamental mechanism for macromolecular structure, function, dynamics and transport. In the chemical and biophysical literature, it is a convention that only those interactions that directly obey the Coulomb's law are referred to the electrostatic (or polar) interactions. All other interactions, including dispersion interactions, steric effects,^{11,17,71,80,103,155} ion-water dipolar interactions, hyperpolarizations, ion-water cluster formation or dissociation, ion spin effects, ion-protein interaction, hydrogen bonds and van der Waals interactions, are referred as non-electrostatic (or nonpolar) interactions, although they are ultimately electrostatic in origin.^{23,164,166} This convention was adopted in our earlier work and is employed in the present work as well.

As in our earlier work, electrostatic modeling is the main focus of the present work. Due to their long range characteristic, electrostatic interactions are modeled as a global quantity that penetrates across domains. Therefore, electrostatic interactions between all domains are considered in the present work. Additionally, although non-electrostatic interactions are relatively short range, their influences near the interfaces can be significant. In particular, the mobile ions in the solvent domain are extremely sensitive to non-electrostatic interactions near the solvent-solute interfaces. Therefore, non-electrostatic interactions between the solvent domain and all macromolecular domains are of primary concern in the present work. Finally, it is well-known that solvent-solvent non-electrostatic interactions, including ion-ion non-electrostatic interactions, play a major role in determining ion microstructures near the solvent-solute interfaces. Therefore, we consider ion-ion non-electrostatic interactions as well. We denote U^S all the non-electrostatic (or nonpolar) interactions involving the solvent (S)

$$U^S = \sum_{\alpha} \rho_{\alpha} U_{\alpha}^S \quad (1)$$

where ρ_{α} is the density of solvent species α and U_{α}^S is given by

$$U_{\alpha}^S = \sum_I \sum_j U_{\alpha j}^{SI}(\mathbf{r}) + \sum_{\beta} U_{\alpha\beta}^{SS}(\mathbf{r}), \quad (2)$$

where $U_{\alpha j}^{SI}(\mathbf{r})$ is the pairwise nonpolar interaction potential between the α th solvent species and j th component in the I th solute domain. Similarly $U_{\alpha\beta}^{SS}(\mathbf{r})$ are the pairwise nonpolar interaction potentials between the α th solvent species and β th solvent species in the solvent domain. These interactions, particularly the ones between solvent species, are important for the understanding of a number of phenomena, such as the solvent polarization, size effects, ζ potentials and solvent microstructures near the solvent-solute interfaces.

For generality, we do not specify the form of U_{α}^S in the present work. We assume that various interactions such as dipole,⁶⁴ multipole,^{89,134} ζ potential and steric effects,¹⁵ are modeled in the present theory by appropriate selections of U_{α}^S . As an example, Lennard-Jones potentials, which have already been employed for $U_{\alpha j}^{SI}(\mathbf{r})$ ³¹ and $U_{\alpha\beta}^{SS}(\mathbf{r})$ ^{23,166} in our earlier work, can be utilized. As pointed out in our earlier work,^{23,31,32,166} these Lennard-Jones potentials involve one or two continuum variables and are significantly different from the conventional Lennard-Jones potential, which traditionally represents short-range interactions between two explicitly labeled particles. Therefore, the resulting formulations involve integral-differential equations. Note that integral equation approaches,^{13,20,50,123,128,157,174} including classical density functional theory,^{68,93,96,115,120,133,161,170,172,173} are quite popular in solvation analysis. Our formulations therefore connect both integral equation and differential equation approaches.

In the rest of this section, we first construct a new multiscale multiphysics and multidomain solvation model in Section II.B. Based on this new model, we further develop corresponding differential geometry based models for charge transport in Section II.C. Finally, we illustrate the flexibility and robustness of the proposed theory by constructing a multiscale multiphysics and multidomain model involving electro-statics, multiple charge species, fluid dynamics, molecular dynamics and elastic dynamics in Section II.D. In the solvent domain, flow convection and viscosity are considered. In the molecular mechanical description, all the bonding and nonbonding interactions in the implicit MD level⁶⁷ are accounted. In the elastic domain, the stress-strain relation is considered.

II.B Multiscale-multiphysics-multidomain model for solvation

Due to the ubiquitous nature of electrostatic interactions and the aqueous environment common to chemical, and biomolecular systems, analysis of molecular solvation is of significant importance in chemistry, biophysics, and medicine. Solvation is a physical process which involves a variety of solvent-solute interactions, such as the electrostatic, dipolar, induced dipolar, hydrogen bonding and van der Waals interactions between the solvent and the solute. Both explicit^{30,121} and implicit models are used to describe the solvation process. Implicit solvent models that treat the solvent as a dielectric continuum, and describe the solute molecule as a static atomistic charge distribution^{3,49,76,85,131,138,160,169} have become popular recently, due to their simplicity and efficiency. Generalized Born,^{7,25,51,66,70,97,114,118,150,152,182} polarizable continuum,^{6,18,38,45,82,113,147,151} Poisson-Boltzmann (PB) models^{49,62,101,138} and nonlocal dielectric methods¹⁷¹ are commonly used. Among them, the PB models are the most popular and can be formally derived from Maxwell's theories.^{12,75,117} A relatively comprehensive descriptions of the solvation process, solvation models and various applications of solvation methods can be found in our two review-style papers.^{31,32}

II.B.1 Total energy functional for solvation

Main direct experimental measurements of solvation include solvation free energy and solvent microstructures near the solvent-solute interface. These measurements validate solvation models. Typically, a solvation model offers either a description of the solvation

free energy or the solvent microstructure. In the present work, we try to develop models for both physical observations.

Nonpolar free energy functional—The solvation free energy can be divided into polar (i.e., electro-static) and nonpolar contributions.^{31,55,156} We propose the following multidomain nonpolar free energy functional

$$G_{\text{nonpolar}} = \sum_I (\gamma_I \text{Area}_I + p_I \text{Vol}_I) + \int_{\Omega_S} U^S d\mathbf{r}, \quad \mathbf{r} \in \mathbb{R}^3, \quad (3)$$

where “Area_{*I*}” and “Vol_{*I*}” are respectively the solute surface area and volume of the *I*th solute domain, $\gamma_I(\mathbf{r})$ is the surface tension, and p_I is the pressure associated with the *I*th solute domain. Here the integration is over the solvent domain Ω_S . In Eq. (3), the first two terms come from the scaled particle theory (SPT), which describes the surface free energy and the mechanical work of creating a cavity of the solute size in the solvent,^{124,144} and the third term describes the solvent-solute interactions.^{31,55,156,164}

To bring the first two terms of Eq. (3) into an Eulerian representation, we utilize the mean surface area for domain Ω_I ¹⁶⁴ and the coarea formula⁵⁹

$$\text{Area}_I = \int_0^1 \int_{S_I^{-1}(c) \cap \Omega_I} d\sigma dc = \int_{\Omega} |\nabla S_I(\mathbf{r})| d\mathbf{r}, \quad \mathbf{r} \in \mathbb{R}^3, \quad (4)$$

where $0 \leq S_I \leq 1$ is a characteristic function or hypersurface function of the solute domain Ω_I . Therefore, the volume of a macromolecular domain in Eq. (3) can be given by

$$\text{Vol}_I = \int_{\Omega_I} d\mathbf{r} = \int_{\Omega} S_I(\mathbf{r}) d\mathbf{r}, \quad (5)$$

where Ω_I is the *I*th macromolecular domain. Note that for adjacent domains, $\Omega_I \cap \Omega_J$ is not empty because each hypersurface function S_I is a smooth function, which leads to the overlapping between Ω_I and Ω_J . We rewrite the last term in Eq. (3) as

$$\int_{\Omega_S} U^S d\mathbf{r} = \int_{\Omega} \left(1 - \sum_I S_I(\mathbf{r}) \right) U^S d\mathbf{r} = \int_{\Omega} S_S(\mathbf{r}) U^S d\mathbf{r}. \quad (6)$$

Polar free energy functional—In our solvation models, the polar solvation free energy is modeled with the Poisson-Boltzmann theory. Sharp and Honig¹³⁷ introduced a variation formulation of the Poisson-Boltzmann equation. The derivation of solvation forces has been given by Gilson *et al*⁶⁹ and others.^{67,164} In our multidomain formalism, we express the polar solvation free energy as

$$G_{\text{polar}} = \int \left\{ \sum_I S_I \left[-\frac{\epsilon_I}{2} |\nabla \Phi|^2 + \Phi \rho_I \right] + S_S \left[-\frac{\epsilon_S}{2} |\nabla \Phi|^2 - k_B T \sum_{\alpha} \rho_{\alpha 0} \left(e^{-\frac{q_{\alpha} \Phi + U_{\alpha}^S - \mu_{\alpha 0}}{k_B T}} - 1 \right) \right] \right\} d\mathbf{r}, \quad (7)$$

where Φ is the electrostatic potential, ϵ_S and ϵ_I are the dielectric functions of the solvent and the *I*th solute, respectively, and ρ_I represents the charge density of the *I*th solute. The form

of ϱ_I depends on the level of the physical description. For example, in the static atomistic description, one has $\varrho_I = \sum_j Q_j^I \delta(\mathbf{r} - \mathbf{r}_j^I)$, with Q_j^I denoting the partial charge of the j th atom in the I th solute. Whereas, charge density ϱ_I takes a continuous form when the domain I is described in a continuous representation. It can also be computed with the density functional theory as demonstrated in our recent work.³³ Here k_B is the Boltzmann constant, T is the temperature, $\rho_{\alpha 0}$ denotes the reference bulk density of the α th solvent species, and q_α is the charge valence of the α th solvent species, which is zero for an uncharged solvent component, such as water molecules.

The Boltzmann distribution in Eq. (7) is of the same form as that in our earlier work and can be derived from the equilibrium condition of the generalized electrochemical potential.¹⁶⁶ Similar to integral equation theories,^{68,129} the potentials U_α^S involve the integration of the continuum variable. By modifying U_α^S term in the Boltzmann distribution, one can easily take into the consideration of dipole,⁶⁴ multi-pole,^{89,134} steric effects,¹⁵ and van der Waals interactions in a generalized Poisson-Boltzmann equation. In the present solvation model, the focus is on a simple description of the solvation free energy and solvent microstructures near the solvent-solute interface. The non-electrostatic interactions between different macromolecular domains have little impact to the equilibrium solvation properties, and thus, are neglected, for simplicity.

The direct combination of polar and nonpolar solvation free energy functionals does not lead to the desirable total free energy functional for solvation. Instead, a modification of the nonpolar energy functional is necessary because the solvent-solute interactions have been accounted in the Boltzmann distribution

$$G_{\text{total}}^{LB-PB}[\{S_I\}, \Phi] = \int \left\{ \sum_I \left[\gamma_I |\nabla S_I| + p_I S_I + S_I \left(-\frac{\epsilon_I}{2} |\nabla \Phi|^2 + \Phi \varrho_I \right) \right] + S_S \left[-\frac{\epsilon_S}{2} |\nabla \Phi|^2 - k_B T \sum_\alpha \rho_{\alpha 0} \left(e^{-\frac{q_\alpha \Phi + U_\alpha^S - \mu_{\alpha 0}}{k_B T}} - 1 \right) \right] \right\} d\mathbf{r}. \quad (8)$$

Here, the first row is the solvation free energy of the solute molecules and the second row is the polar solvation free energy of the solvent. Equation (8) provides a starting point for our variational analysis.

II.B.2 Governing equations for solvation

Established in a series of work,^{21,31,32,164,166} the variation of the solvation free energy functional (8) is quite standard. The derivation of two governing equations is discussed below.

Multidomain Laplace-Beltrami equations—In our formalism, the surfaces of biomolecular complexes are described by hypersurface functions $\{S_I\}$, which are governed by generalized Laplace-Beltrami equations. The total solvation free energy/in Eq. (8) is a functional of hypersurface functions $\{S_I\}$ and electrostatic potential Φ . By using the Euler-Lagrange equation, we have

$$\frac{\delta G_{\text{total}}^{LB-PB}}{\delta S_I} \Rightarrow -\nabla \cdot \left(\gamma_I \frac{\nabla S_I}{|\nabla S_I|} \right) + p_I - \frac{\epsilon_I}{2} |\nabla \Phi|^2 + \Phi \quad \varrho_I + \frac{\epsilon_S}{2} |\nabla \Phi|^2 + k_B T \sum \rho_{\alpha 0} \left(e^{-\frac{q_{\alpha} \Phi + U_{\alpha}^S - \mu_{\alpha 0}}{k_B T}} - 1 \right) = 0. \quad (9)$$

It is convenient to introduce an artificial time^{10,31,32,164} to arrive at the following generalized Laplace-Beltrami equations

$$\frac{\partial S_I}{\partial t} = |\nabla S_I| \left[\nabla \cdot \left(\gamma_I \frac{\nabla S_I}{|\nabla S_I|} \right) + V_I^{LB-PB} \right], \quad I=1, \dots, N, \quad (10)$$

where the potential driven terms are given by

$$V_I^{LB-PB} = -p_I + \frac{\epsilon_I}{2} |\nabla \Phi|^2 - \Phi \quad \varrho_I - \frac{\epsilon_S}{2} |\nabla \Phi|^2 - k_B T \sum_{\alpha} \rho_{\alpha 0} \left(e^{-\frac{q_{\alpha} \Phi + U_{\alpha}^S - \mu_{\alpha 0}}{k_B T}} - 1 \right). \quad (11)$$

Generalized Laplace-Beltrami equations (10) determine not only the solvent-solute interfaces but also the solute-solute interfaces. It is possible for many domains to overlap at one particular point of the space. Technically, there is some similarity between the present multidomain Laplace-Beltrami flows and the phase field theory based multi-component multiphase fluid flows,⁹² despite of their major conceptual differences.

Multidomain Poisson-Boltzmann equation—Variation with respect to electrostatic potential Φ leads to

$$\frac{\delta G_{\text{total}}^{LB-PB}}{\delta \Phi} \Rightarrow \nabla \cdot \left(\left[S_S \epsilon_S + \sum_I S_I \epsilon_I \right] \nabla \Phi \right) + \sum_I S_I \varrho_I + S_S \sum_{\alpha} q_{\alpha} \rho_{\alpha 0} e^{-\frac{q_{\alpha} \Phi + U_{\alpha}^S - \mu_{\alpha 0}}{k_B T}} = 0. \quad (12)$$

From Eq. (12), one has the multidomain Poisson-Boltzmann equation

$$-\nabla \cdot (\epsilon(S) \nabla \Phi) = \sum_I S_I \varrho_I + S_S \sum_{\alpha} q_{\alpha} \rho_{\alpha 0} e^{-\frac{q_{\alpha} \Phi + U_{\alpha}^S - \mu_{\alpha 0}}{k_B T}}, \quad (13)$$

where $\epsilon(S) = S_S \epsilon_S + \sum_I S_I \epsilon_I$ is the generalized permittivity function for a multidomain setting. It reduces to the form discussed in our earlier work^{31,164} when there is only one solute domain. As described in our earlier work, $\epsilon(S)$ is a smooth dielectric function. The

Boltzmann factor $e^{-\frac{U_{\alpha}^S}{k_B T}}$ in Eq. (13) gives rise to a non-electrostatic correction to the charge density near the interface. Therefore, it can be used to describe solvent microstructures near the solvent-solute interface.

In our formulation, Eqs. (10) and (13) govern the surface evolution and the electrostatic potential, respectively. We denote these coupled equations the Laplace-Beltrami and Poisson-Boltzmann (LB-PB) equations. When there is only one solute domain, these equations reduce to their corresponding forms obtained in our earlier work.¹⁶⁶

The solvation model describes the system at equilibrium. However as the charge density is approximated by the Boltzmann distribution, which involves appropriate integrals in the

potential U_{α}^S ,^{23,166} the generalized Poisson-Boltzmann equation, Eq. (13), is in fact an integral-differential equation. The solution of Eq. (13) needs to be carried out iteratively for realistic problems.

II.C Multiscale-multiphysics-multidomain model for charge transport

Solvation models are for systems at equilibrium, in which ion densities can be efficiently approximated by the Boltzmann distribution. However, for non-equilibrium systems, such as charge transport in fuel cells, solar cells, nano-fluidics, ion channels, gap junctions and neuron synapses, an independent description of ion densities is required. A wide variety of transport theories have been developed, ranging from Boltzmann kinetics,^{16,37,73,141,158} Monte Carlo approach,⁸⁴ Fokker-Planck and Master equations,^{60,83} non-equilibrium Green's function,^{22,47,48,87,100,136,145} coupled Navier-Stokes and Poisson-Boltzmann (PB) equations,¹²⁶ to Poisson-Nernst-Planck (PNP) equations.^{4,26,57,61,98,110,140} Among these approaches, the PNP model is relatively simple, and able to offer very good predictions of current-voltage curves for many channel proteins.^{19,98,177} However, the PNP theory neglects the finite size effect due to its continuum representation of ion densities.^{17,44,80,86,90,106,110,139} Advantages and limitations of the aforementioned transport models have been discussed in the literature.^{2,5,35,36,40–42,42,54,57,58,99,104,105,111,130,135,154} The reader is referred to Ref¹⁶⁶ for a recent review.

Differential geometry based charge transport models have been introduced in our earlier work.¹⁶⁴ Extension to proton transport and validation with experimental data have been carried out recently.^{21,23,166} A major feature of our differential geometry based charge transport models is that they combine the transport modeling with the geometric flow based surface modeling so as to generate self-consistent solvent-solute interfaces.¹⁶⁴ Another important feature of our transport models is that they unify the transport modeling with the solvation modeling. As a result, our nonequilibrium transport models reduce to corresponding equilibrium solvation models at equilibrium.¹⁶⁶ In the next subsection, we provide a multidomain generalization of our earlier transport formalism.

II.C.1 Total energy functional for a system with charged species

Charge transport involves material exchange and thus chemical potential(s). In nonequilibrium thermodynamics, chemical potential related free energy can be expressed as¹⁶⁶

$$G_{\text{chem}} = \int \sum_{\alpha} \left\{ (\mu_{\alpha}^0 - \mu_{\alpha 0}) \rho_{\alpha} + k_B T \rho_{\alpha} \ln \frac{\rho_{\alpha}}{\rho_{\alpha 0}} - k_B T (\rho_{\alpha} - \rho_{\alpha 0}) \right\} d\mathbf{r}, \quad (14)$$

where μ_{α}^0 is a reference chemical potential of the α th species at which the associated ion density is $\rho_{\alpha 0}$ given $\Phi = U_{\alpha}^S = \mu_{\alpha 0} = 0$. The second term is associated with entropy of mixing, and the last term is for relative osmotic.¹¹²

To construct a total energy functional for charge transport, we need to recognize that the densities of ion species do not obey the Boltzmann distribution. We therefore utilize the

nonpolar free energy functional (3), and modify the source term of the solvent polar energy functional (7). Together with chemical potential related free energy (14), the total free energy functional for the charge transport is given by

$$G_{\text{total}}^{LB-PNP} [\{S_I\}, \Phi, \{\rho_\alpha\}] = f \left\{ \sum_I (\gamma_I |\nabla S_I| + p_I S_I) + S_s U^S + \sum_I S_I \left[-\frac{\epsilon_I}{2} |\nabla \Phi|^2 + \Phi \varrho_I \right] + S_s \left[-\frac{\epsilon_s}{2} |\nabla \Phi|^2 + \Phi \sum_\alpha \rho_\alpha q_\alpha \right] + S_s \sum_\alpha \left[(\mu_\alpha^0 - \mu_{\alpha 0}) \rho_\alpha + k_B T \rho \right] \right\} \quad (15)$$

where the first row is the nonpolar solvation free energy functional for our multidomain description, the second row is the polar (electrostatic) solvation free energy functional, and the last row is the chemical potential related energy functional for charge transport. We denote λ_α a Lagrange multiplier for ensuring appropriate physical properties at equilibrium.^{61,166}

II.C.2 Governing equations

As functionals of hypersurface functions $\{S_I\}$, electrostatic potential and ion densities $\{\rho_\alpha\}$, the total free energy (15) can be minimized by using the variational principle, which gives rise to desirable governing equations for the system, namely, partial differential equations (PDEs) for $\{S_I\}$, Φ and $\{\rho_\alpha\}$. The solution of these PDEs in turn minimizes the total free energy in Eq. (15).

Multidomain Laplace-Beltrami equations—As discussed in the last subsection, hypersurface functions $\{S_I\}$ are governed by generalized Laplace-Beltrami equations. These equations are different in their source terms. We apply the Euler-Lagrange equation to $\{S_I\}$ to have

$$\begin{aligned} \frac{\delta G_{\text{total}}^{LB-PNP}}{\delta S_I} &\Rightarrow \nabla \cdot \left(\gamma_I \frac{\nabla S_I}{|\nabla S_I|} \right) \\ &+ p_I - U^S - \sum_I \left(\frac{\epsilon_I}{2} |\nabla \Phi|^2 + \Phi \varrho_I \right) \\ &+ \frac{\epsilon_s}{2} |\nabla \Phi|^2 - \Phi \sum_\alpha \rho_\alpha q_\alpha \\ &- \sum_\alpha \left[-\mu_{\alpha 0} \rho_\alpha + k_B T \rho_\alpha \ln \frac{\rho_\alpha}{\rho_{\alpha 0}} - k_B T (\rho_\alpha - \rho_{\alpha 0}) \right] = 0. \end{aligned} \quad (16)$$

By using the same procedure as that used in our earlier work,^{8,164} we arrive at a set of N Laplace-Beltrami equations:

$$\frac{\partial S_I}{\partial t} = |\nabla S_I| \left[\nabla \cdot \left(\gamma_I \frac{\nabla S_I}{|\nabla S_I|} \right) + V^{LB-PNP} \right], \quad I=1, \dots, N, \quad (17)$$

where

$$V^{LB-PNP} = -p_I + U^S + \sum_I \left(\frac{\epsilon_I}{2} |\nabla \Phi|^2 - \Phi \varrho_I \right) - \frac{\epsilon_s}{2} |\nabla \Phi|^2 + \Phi \sum_\alpha \rho_\alpha q_\alpha + \sum_\alpha \left[k_B T \left(\rho_\alpha \ln \frac{\rho_\alpha}{\rho_{\alpha 0}} - \rho_\alpha + \rho_{\alpha 0} \right) - \mu_{\alpha 0} \rho_\alpha \right]. \quad (18)$$

Multidomain Poisson equation—We first carry out the variation of the total free energy functional with respect to the electrostatic potential Φ

$$\frac{\delta G_{\text{total}}^{LB-PNP}}{\delta \Phi} \Rightarrow \nabla \cdot \left(\left[S_S \epsilon_S + \sum_I S_I \epsilon_I \right] \nabla \Phi \right) + \sum_I S_I \varrho_I + S_S \sum_{\alpha} \rho_{\alpha} q_{\alpha} = 0. \quad (19)$$

This gives rise to the desirable multidomain Poisson equation

$$-\nabla \cdot (\epsilon(S) \nabla \Phi) = \sum_I S_I \varrho_I + S_S \sum_{\alpha} \rho_{\alpha} q_{\alpha}, \quad (20)$$

where $\epsilon(S) = S_S \epsilon_S + \sum_I S_I \epsilon_I$ is an interface dependent dielectric profile, which is a continuous function. Obviously, Eq. (20) involves hypersurface functions S_I and densities of ions ρ_{α} . The latter is determined by a set of PDEs, instead of a Boltzmann factor, in the present formulation.

Multidomain Nernst-Planck equations—The derivation of Nernst-Planck equations is similar to that described in our earlier work.¹⁶⁶ Let us carry out the variation with respect to ion densities $\{\rho_{\alpha}\}$

$$\frac{\delta G_{\text{total}}^{LB-PNP}}{\delta \rho_{\alpha}} \Rightarrow \mu_{\alpha}^{gen} = \mu_{\alpha}^0 - \mu_{\alpha 0} + k_B T \ln \frac{\rho_{\alpha}}{\rho_{\alpha 0}} + q_{\alpha} \Phi + U_{\alpha}^S + \lambda_{\alpha} \quad (21)$$

where μ_{α}^{gen} is the relative generalized potential of species α and vanishes at equilibrium, which gives rise to

$$\lambda_{\alpha} = -\mu_{\alpha}^0 \quad \text{and} \quad \rho_{\alpha} = \rho_{\alpha 0} e^{-\frac{q_{\alpha} \Phi + U_{\alpha}^S - \mu_{\alpha 0}}{k_B T}}. \quad (22)$$

It is seen that the generalized Boltzmann factor used in the last subsection is justified by equilibrium condition (22).

For charge transport, the system is of non-equilibrium in general due to inhomogeneities in ion densities and electrostatic potential. In many situations, these inhomogeneities originate from boundary conditions, such as concentration gradient between intercellular and extracellular ions, and electrostatic potential gradient due to applied voltages in nanofluidic devices and patch clamps. We construct a set of ion flux equations by using Nernst-Einstein

equation $\mathbf{J}_{\alpha} = -D_{\alpha} \rho_{\alpha} \nabla \frac{\mu_{\alpha}^{gen}}{k_B T}$ with D_{α} being the diffusion coefficient of species α . In fact, D_{α} needs to be a position dependent function in many applications, such as ion channels.¹⁷⁷ By taking into consideration of Eq. (22), the relative generalized potential μ_{α}^{gen} is given by

$\mu_{\alpha}^{gen} = k_B T \ln \frac{\rho_{\alpha}}{\rho_{\alpha 0}} + q_{\alpha} \Phi + U_{\alpha}^S - \mu_{\alpha 0}$. We further make use of Fick's law of diffusion

$\frac{\partial \rho_{\alpha}}{\partial t} = -\nabla \cdot \mathbf{J}_{\alpha}$ to arrive at desirable Nernst-Planck equations

$$\frac{\partial \rho_{\alpha}}{\partial t} = \nabla \cdot \left[D_{\alpha} \left(\nabla \rho_{\alpha} + \frac{\rho_{\alpha}}{k_B T} \nabla (q_{\alpha} \Phi + U_{\alpha}^S) \right) \right], \quad (23)$$

where $q_\alpha \Phi + U_\alpha$ can be regarded as a mean field potential, which gives rise a generalized convection (force) term in the ion density dynamics. This approach, namely, the construction of a flow flux from the energy minimization, is often called a gradient flow method in the literature.

At steady state, Eq. (23) becomes

$$\nabla \cdot \left[D_\alpha \left(\nabla \rho_\alpha + \frac{\rho_\alpha}{k_B T} \nabla (q_\alpha \Phi + U_\alpha^S) \right) \right] = 0. \quad (24)$$

The solution of Eq. (23) depends on Φ , i.e., the solution of the multidomain Poisson equation (20). We call Eqs. (20) and (23) the generalized Poisson-Nernst-Planck (PNP) equations. Note that the solution of Eq. (20) depends on hypersurface functions S_I .

The multidomain Laplace-Beltrami equations (17) and PNP equations (20) and (23) constitute a coupled system, and are called generalized LB-PNP equations. Their solution minimizes the total free energy functional (15) for charge transport. Unlike the traditional PNP equations, the present LB-PNP equations self-consistently couple biomolecular surfaces and dielectric profiles with electrostatic potentials and ion densities. Additionally, the general interaction potential U^S include possible solvent-solute and ion-ion interactions, which endows the present LB-PNP formalism with the capability of predicting ion microstructures near solvent-solute interfaces. Finally, the multidomain setting in the present formulation further allows the flexibility of modeling multiple material compositions.

II.C.3 Consistency with the multidomain solvation model

In our earlier work, we have shown both theoretically and numerically that the non-equilibrium LB-PNP model reduces to the equilibrium solvation model at equilibrium.¹⁶⁶ This consistency between a non-equilibrium theory and an equilibrium one is essential in theoretical modeling and our understanding of non-equilibrium dynamics. In the present multidomain modeling, we demonstrate further that this important consistency can also be established.

To this end, we apply the constraints in Eq. (22) to the total free energy functional in Eq. (15)

$$G_{\text{total}}^{LB-PNP} = \int \left\{ \sum_I (\gamma_I |\nabla S_I| + p_I S_I) + S_s U^S + \sum_I S_I \left[-\frac{\epsilon_I}{2} |\nabla \Phi|^2 + \Phi \varrho_I \right] + S_s \left[-\frac{\epsilon_s}{2} |\nabla \Phi|^2 + \Phi \sum_\alpha \rho_\alpha q_\alpha \right] + S_s \sum_\alpha \left[(\mu_\alpha^0 - \mu_{\alpha 0}) \rho_\alpha + k_B T \rho_\alpha \right] \right\}$$

Additionally, for the surface driven functions of the generalized LB equation, it is easy to show that under the constraints of Eq. (22), one has $V^{LB-PNP} \rightarrow V^{LB-PB}$. Furthermore, under the constraints of Eq. (22), $\mathbf{J}_\alpha = -D_\alpha \rho_\alpha \nabla \frac{\mu_\alpha^{gen}}{k_B T} = 0$ and PNP equations (20) vanish. Therefore, we fully recover the equilibrium LB-PB model from the non equilibrium LB-PNP theory at equilibrium.

II.D Chemo-Electro-Fluid-MD-Elastic model

Many chemical, physical and biological systems are excessively large and involve a huge number of degrees of freedom. As such, their atomic description is intractable with current computer capability. Subcellular organelles, molecular motors, virus particles and fuel cells are examples of excessively large aqueous systems. Theoretical modeling, analysis and simulation of these systems pose a fabulous challenge to the research community. Multiscale, multiphysics and multidomain methods proposed in this work provide potential tactics and strategies for this class of excessively large problems.

In this subsection, we demonstrate the use of the present multidomain theory by considering a system with three distinguished domains, a solvent domain and two molecular domains. The solvent domain is described in terms of the fluid mechanics. One of the molecular domain is treated with the molecular dynamics (or coarse grained dynamics) and the other molecular domain is furnished by using the elastic dynamics. Two molecular domains are directly coupled to each other via electrostatic interactions. Additionally, both molecular domains are strongly coupled to the solvent domain via electrostatic interactions as well as general solvent-solute non-electrostatic interactions described by U^S .

II.D.1 The action functionals

Fluid dynamics—Fluid flows play an important role in nanofluidic devices and fuel cell systems. In nanofluidics, fluids are controlled and manipulated at submicrometer and nanometer scales to study the behavior of molecular and biological systems. At such scales, the characteristic length scale of the fluid coincides with the length scale of the biomolecule and the scale of the Debye length. As a result, fluids show interesting behaviors which are not observed in larger scales. Micro/nano fluidic apparatuses have been developed for basic measurements, ranging from molecular diffusion coefficients,⁸⁸ pH values,^{109,167} chemical binding affinities,⁸⁸ to enzyme reaction kinetics.^{53,72} As a new technology, nanofluidics has been devised for polymerase chain reaction (PCR) amplifications,¹⁴ macromolecule accumulator,^{39,168} electrokinetics,¹¹ biomaterial separation⁹¹ membrane protein crystallization,¹⁰⁷ single nucleotide polymorphism genotyping,¹⁵⁹ and gene expression analysis via DNA computing.¹⁷⁵ The influence domain of electrostatic potentials in

nanofluidic systems is characterized by the Debye length $\lambda_D = \sqrt{\epsilon_s k_B T / \sum_{\alpha} \rho_{\alpha 0} q_{\alpha}^2}$, which varies dramatically from the channels of transmembrane proteins, pores of proton exchange membranes, to clefts of neuron synapses. To model electro-osmosis and electrophoresis, it is necessary to combine fluid mechanics with electrostatic analysis.

We consider multicomponent homogeneous incompressible flows. The Lagrangian of an incompressible viscous flow was discussed in our earlier work.¹⁶⁴ It consists of kinetic energy, potential energy and viscous energy lost due to friction¹⁶⁴

$$L_{\text{Fluid}} = \int (1 - S) \left[\rho \frac{\mathbf{v}^2}{2} - \left(\Psi + p_s + U^S - \frac{\mu_f}{8} \int^t \left(\frac{\partial \mathbf{v}_i}{\partial \mathbf{x}_j} + \frac{\partial \mathbf{v}_j}{\partial \mathbf{x}_i} \right)^2 dt' \right) \right] d\mathbf{x}, \quad (26)$$

where $\rho = \sum_{\alpha} \rho_{\alpha}$ is the total solvent density for a multicomponent homogeneous flow, p_S is the hydrodynamic pressure, \mathbf{v} is the flow stream velocity, v_i are velocity components and μ_f is the viscosity of the fluid. Here, Ψ is the potential energy mostly due to the gravitation. The last term in Eq. (26) is the stress energy density

$$E_{\text{Stress}} = \frac{\mu_f}{8} \int^t \left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right)^2 dt' = \frac{1}{2\mu_f} \int^t \mathbb{T}^2 dt', \quad (27)$$

where \mathbb{T} is the stress tensor. The Einstein summation convention is used in the above expression. Obviously, the stress tensor is symmetric

$$\mathbb{T}_{ij} = \mathbb{T}_{ji}. \quad (28)$$

The reader is referred to Ref.¹⁶⁴ for more detailed discussion of the fluid energy functional. In the present work, we slightly modify Eq. (26) to avoid redundancy in energy density functional.

Molecular dynamics—Unlike the macroscopic fluid dynamics, the molecular mechanics seeks microscopic atomistic or coarse grained descriptions of a solute component, which is typically crucial to the physics of interest. For example, the structure and dynamics of an ion channel protein is the key to the understanding of the channel gating mechanism. Molecular dynamics can be employed to obtain structure information due to mutations. The molecular mechanics in the present formulation is akin to the implicit molecular dynamics proposed in the earlier work by Gilson et al⁶⁹ and others,^{81,108} including ours.⁶⁷

The energy functional of a molecular mechanics was introduced in our earlier work.¹⁶⁴ The Lagrangian of molecular mechanics includes the kinetic energy of each individual atom or particle and the potential energy due to various microscopic interactions¹⁶⁴

$$L_{MD} = \int \int S \sum_j \left[\rho_j \frac{\dot{\mathbf{z}}_j^2}{2} - U^M(\mathbf{z}) \right] dx dz \quad (29)$$

where $\rho_j = m_j \delta(\mathbf{z}_j - \mathbf{x}_j)$ is the mass density of the j th atom or particle in a coarse grained description, m_j and \mathbf{x}_j are the mass and the macroscopic position of the j th atom or particle, respectively. Here $\rho_j \frac{\dot{\mathbf{z}}_j^2}{2}$ and $U^M(\mathbf{z})$ are respectively the kinetic and the potential energy densities of the j th atom or particle with $\dot{\mathbf{z}}_j = \frac{d\mathbf{z}_j}{dt}$. Additionally, we denote $\mathbf{z} = (\mathbf{z}_1, \mathbf{z}_2, \dots, \mathbf{z}_{N_a}) \in \mathbb{R}^{3N_a}$ as the microscopic variable of N_a atoms or particles and $d\mathbf{z} = dz_1 dz_2 \dots dz_{N_a}$. In principle, the potential interactions U^M include all bonding and nonbonding components used in implicit MD calculations.^{67,108}

Elastic dynamics—The microscopic domain described above is complemented with an elastic domain to dramatically reduce the number of degrees of freedom. Both fluid dynamics and electrostatic interactions will be coupled to molecular dynamics and elastic dynamics. Some pioneer work on fluid-structure coupling was due to Peskin.¹²² The coupling of electrostatics and elasticity was considered by Zhou et al¹⁸¹ for biomolecules.

Alternatively, phase field⁵² and Helfrich curvature¹¹⁹ approaches of the elastic bending energy for vesicle membranes were discussed in the literature.

Let us consider a point \mathbf{r} in \mathbb{R}^3 that is deformed to $\bar{\mathbf{r}}$ due to a displacement \mathbf{w} , i.e.,

$$\mathbf{w} = \bar{\mathbf{r}} - \mathbf{r}. \quad (30)$$

The deformation can be characterized by a strain tensor¹⁶⁴

$$\sigma_{ij} = \frac{1}{2} \left[\frac{\partial \mathbf{w}_i}{\partial \mathbf{r}_j} + \frac{\partial \mathbf{w}_j}{\partial \mathbf{r}_i} \right], \quad (31)$$

where the nonlinear term in \mathbf{w} is omitted for relatively small deformations.¹⁶⁴ This linear elasticity analysis has been widely used. The Einstein summation notation is used in the above expression.

For an isotropic system, the elastic potential energy density takes the form

$$E_{\text{Elastic}} = \frac{1}{2} \left[\lambda_E \sigma_{ii}^2 + \mu_E (\sigma_{ij})^2 \right], \quad (32)$$

where λ_E is the elastic modulus or stress/strain ratio, and μ_E is the shear modulus. Both the elastic modulus λ_E and the shear modulus μ_E are connected to the atomic or molecular interaction strengths.

Additionally, the kinetic energy density can be expressed as $\frac{\rho_E}{2} \dot{\mathbf{w}}^2$, where ρ_E is the mass density of the elastic macromolecule and $\dot{\mathbf{w}}$ is the velocity of the displacement. Therefore, the Lagrangian of the elastic system is given as the difference of the kinetic energy and the potential energy

$$L_{\text{Elastic}} = \int S \left[\frac{\rho_E}{2} \dot{\mathbf{w}}^2 - \frac{1}{2} \left(\lambda_E \sigma_{ii}^2 + \mu_E (\sigma_{ij})^2 \right) \right] d\mathbf{r}. \quad (33)$$

Total action functional—Total action functional of the present multidomain system involves energy densities from differential physics, namely, polar and nonpolar solvation, chemical mixing, fluid dynamics, molecular dynamics and elastic dynamics. However, we need to eliminate any redundancy in energy densities. We consider the following total action functional

$$G_{\text{total}}^{MD-FD-ED} [S, \Phi, \{\rho_\alpha\}] = \iiint \left\{ \gamma_M |\nabla S_M| + \gamma_E |\nabla S_I| + p_M S_M + p_E S_E + S_S U^S + S_M \left[-\frac{\epsilon_M}{2} |\nabla \Phi|^2 + \Phi \rho_M \right] + S_E \left[-\frac{\epsilon_E}{2} |\nabla \Phi|^2 + \Phi \rho_E \right] + S_S \left[-\frac{\epsilon_S}{2} |\nabla \Phi|^2 \right] \right\} d\mathbf{r} \quad (34)$$

where expressions from the first to the last row in Eq. (34) are respectively the multidomain nonpolar free energy, electrostatic energy, chemical potential related energy, fluid dynamics energy, molecular dynamics energy and elastic dynamics energy.

II.D.2 Governing equations

We derive governing equations by a total variation in the present case.¹⁶⁴ A number of coupled PDEs are obtained as described below.

Generalized Laplace-Beltrami equation—By using the same procedure as that used in the earlier sections, we end up with two generalized Laplace-Beltrami equations, one for the molecular mechanics domain and the other for the elastic domain

$$\frac{\partial S_I}{\partial t} = \frac{|\nabla S_I|}{|\nabla S_I|} \left[\nabla \cdot \left(\gamma_I \frac{\nabla S_I}{|\nabla S_I|} \right) + V_I \right], \quad I=M, E, \quad (35)$$

where driven terms V_M and V_E are respectively given by

$$\begin{aligned} V_M = & -p_M + U^S + \frac{\epsilon_M}{2} |\nabla \Phi|^2 - \Phi \varrho_M \\ & - \frac{\epsilon_S}{2} |\nabla \Phi|^2 + \Phi \sum_{\alpha} \rho_{\alpha} q_{\alpha} \\ & + \sum_{\alpha} \left[k_B T \left(\rho_{\alpha} \ln \frac{\rho_{\alpha}}{\rho_{\alpha 0}} - \rho_{\alpha} + \rho_{\alpha 0} \right) - \mu_{\alpha 0} \rho_{\alpha} \right] \\ & - \left[\rho \frac{\mathbf{v}^2}{2} - p_S + \frac{\mu_f}{8} \int^t \left(\frac{\partial \mathbf{v}_i}{\partial \mathbf{r}_j} + \frac{\partial \mathbf{v}_j}{\partial \mathbf{r}_i} \right)^2 dt' \right] \\ & + \sum_j \left[\rho_j \frac{\dot{\mathbf{z}}_j^2}{2} - U^M(\mathbf{z}) \right]. \end{aligned} \quad (36)$$

and

$$\begin{aligned} V_E = & -p_E + U^S + \frac{\epsilon_E}{2} |\nabla \Phi|^2 - \Phi \varrho_E \\ & - \frac{\epsilon_S}{2} |\nabla \Phi|^2 + \Phi \sum_{\alpha} \rho_{\alpha} q_{\alpha} \\ & + \sum_{\alpha} \left[k_B T \left(\rho_{\alpha} \ln \frac{\rho_{\alpha}}{\rho_{\alpha 0}} - \rho_{\alpha} + \rho_{\alpha 0} \right) - \mu_{\alpha 0} \rho_{\alpha} \right] \left[\rho \frac{\mathbf{v}^2}{2} - p_S + \frac{\mu_f}{8} \int^t \left(\frac{\partial \mathbf{v}_i}{\partial \mathbf{r}_j} + \frac{\partial \mathbf{v}_j}{\partial \mathbf{r}_i} \right)^2 dt' \right] \\ & + \left[\frac{\rho_E}{2} \dot{\mathbf{w}}^2 - \frac{1}{2} \left(\lambda_E \sigma_{ii}^2 + \mu_E (\sigma_{ij})^2 \right) \right]. \end{aligned} \quad (37)$$

The above two expressions differ in their electrostatic energies and their last terms, which are associated with specific dynamic descriptions. Solution to these equations determines S_M and S_E , as well as S_S , because of $S_S = 1 - S_M - S_E$.

Generalized Poisson equation—The variation of the total action functional (34) with respect to Φ leads to the generalized Poisson equation

$$-\nabla \cdot (\epsilon(S) \nabla \Phi) = S_M \varrho_M + S_E \varrho_E + S_S \sum_{\alpha} \rho_{\alpha} q_{\alpha} \quad (38)$$

where $\epsilon(S) = S_S \epsilon_S + S_M \epsilon_M + S_E \epsilon_E$ is the generalized permittivity function. Obviously, Eq. (38) is a special case of Eq. (20).

Generalized Nernst-Planck equation—With a non-vanishing flow velocity, the derivation of the generalized Nernst-Planck is slightly different from that in Section II.C.2, but is very similar to that discussed in our earlier work.¹⁶⁶ The variation of the total action functional (34) with respect to ion densities ρ_α gives rise to a generalized relative potential μ_α^{gen}

$$\mu_\alpha^{gen} = k_B T \ln \frac{\rho_\alpha}{\rho_{\alpha 0}} + q_\alpha \Phi + U_\alpha^S - \mu_{\alpha 0} - \frac{\mathbf{v}^2}{2}. \quad (39)$$

We use Eq. (39) to construct a generalized flux

$$\mathbf{J}_\alpha = -D_\alpha \rho_\alpha \nabla \frac{\mu_\alpha^{gen}}{k_B T}. \quad (40)$$

The generalized Fick's law, which takes care of chemical reactions and incompressible fluid flows, gives^{164,166}

$$\frac{\partial \rho_\alpha}{\partial t} + \mathbf{v} \cdot \nabla \rho_\alpha = -\nabla \cdot \mathbf{J}_\alpha + \sum_j \bar{\nu}_{\alpha j} J^j \quad (41)$$

where $\bar{\nu}_{\alpha j} J^j$ is the density production of α species per unit volume in the j th chemical reaction.¹⁶⁴ Explicitly, the generalized Nernst-Planck equation reads

$$\frac{\partial \rho_\alpha}{\partial t} + \mathbf{v} \cdot \nabla \rho_\alpha = \nabla \cdot D_\alpha \left[\nabla \rho_\alpha + \frac{\rho_\alpha}{k_B T} \nabla \left(q_\alpha \Phi + U_\alpha^S - \frac{\mathbf{v}^2}{2} \right) \right] + \sum_j \bar{\nu}_{\alpha j} J^j. \quad (42)$$

Equation (42) provides a generalized mass conservation where the rate of change of the α th ion species is balanced by the convective transport of the incompressible multicomponent fluid flow, density gradient, electrostatic gradient, potential forces due to solvent-solute interactions, solvent-solvent interactions, the flux of the fluid kinetic energy, and finally, chemical reactions. Equation (42) reduces to Eq. (23) when the velocity and the chemical reaction flux vanish.

Generalized Navier-Stokes equation—The conservation equation for flow stream velocity of incompressible flows can also be derived from variational principle.^{164,166} The total variation of total action functional (34) leads to the generalized Navier-Stokes equation

$$\rho \left(\frac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v} \right) = -\nabla p_s + \frac{1}{S_s} \nabla \cdot S_s \mathbb{T} + \mathbf{F}_E, \quad (43)$$

where flow stress tensor \mathbb{T} can be expressed as

$$\mathbb{T} = \frac{\mu_f}{2} \left(\frac{\partial \mathbf{v}_i}{\partial \mathbf{r}_j} + \frac{\partial \mathbf{v}_j}{\partial \mathbf{r}_i} \right) = \frac{\mu_f}{2} \left[\nabla \mathbf{v} + (\nabla \mathbf{v})^T \right], \quad (44)$$

where symbol T denotes the transpose. In Eq. (43), \mathbf{F}_E is the total force given by

$$\mathbf{F}_E = \frac{1}{1 - S_M - S_E} \left(-S_M \nabla p_M - S_E \nabla p_E - S_S \sum_{\alpha} \rho_{\alpha} \nabla U_{\alpha}^S + \varrho_M \nabla (S_M \Phi) + \varrho_E \nabla (S_E \Phi) \right) \quad (45)$$

Equation (45) reduces to the standard Navier-Stokes at the inner solvent domain (i.e., $S_M = S_E = 0$), except for an extra force term $-\sum_{\alpha} \rho_{\alpha} \nabla U_{\alpha}^S$, which is due to the consideration of solvent-solvent interactions. In our earlier work,¹⁶⁴ we discussed the reduction of the two-domain version of Eq. (45) to the Stokes equation, which is relevant for biomolecular systems. The connection of the two-domain version of Eq. (45) with the Navier-Stokes equation for classical electroviscous flows was also discussed.¹⁶⁶

Generalized Newton equation—As discussed in our earlier work,¹⁶⁴ part of the total variation is associated with $\delta \mathbf{z}_j$, which gives rise to the desirable Newton's equation for the molecular dynamics (MD)

$$\rho_j \ddot{\mathbf{z}}_j = \mathbf{f}^j, \quad j=1, 2, \dots, N^a, \quad (46)$$

where $\{\mathbf{f}^j\}$ are a set of forces associated with solvent-solute interaction near the interfaces and molecular interactions. We have that $\mathbf{f}^j = \mathbf{f}_{SSI}^j + \mathbf{f}_{RF}^j + \mathbf{f}_{PI}^j$ with the components given as

$$\mathbf{f}_{SSI}^j = -\frac{S_S}{S_M} \nabla_j U^S \quad (47)$$

$$\mathbf{f}_{RF}^j = \frac{1}{S_M} (\varrho_M \nabla_j (S_M \Phi) + \varrho_E \nabla_j (S_E \Phi)) \quad (48)$$

$$\mathbf{f}_{PI}^j = -\nabla_j U^M(\mathbf{z}), \quad (49)$$

where \mathbf{f}_{SSI}^j , \mathbf{f}_{RF}^j and \mathbf{f}_{PI}^j are respectively, solvent-solute interaction force, reaction field force and potential interaction force due to atomic or particle interactions.

Elastic dynamics—The variation of the total action functional also leads to the governing equation for the elastic dynamics of the macromolecule

$$\rho_E \ddot{\mathbf{w}} = \frac{1}{S_E} [(\lambda_E + \mu_E) \nabla S_E \nabla \cdot \mathbf{w} + \mu_E \nabla \cdot S_E \nabla \mathbf{w}] + \mathbf{f}^E. \quad (50)$$

where $\mathbf{f}^E = \mathbf{f}_{SSI}^E + \mathbf{f}_{RF}^E$ are the forces acting on the elastic macromolecule. The fluid-structure interaction (FSI) force \mathbf{f}_{FSI}^E and reaction field (RF) force \mathbf{f}_{RF}^E are given by

$$\mathbf{f}_{FSI}^E = -\frac{S_S}{S_E} \sum_{\alpha} \rho_{\alpha} \nabla_{\mathbf{w}} U_{\alpha}^S \quad (51)$$

$$\mathbf{f}_{RF}^E = -\frac{1}{S_E} \Phi (S_M \nabla_{\mathbf{w}} \varrho_M + S_E \nabla_{\mathbf{w}} \varrho_E). \quad (52)$$

To understand Eq. (50), we define the stress tensor of the elastic material as¹⁶⁴

$$\mathbb{T}_{ij}^E = \lambda_E \sigma_{ii} \delta_{ij} + 2\mu_E \sigma_{ij}. \quad (53)$$

We therefore finally rewrite Eq. (50) as

$$\rho_E \ddot{\mathbf{w}} = \frac{1}{S_E} \nabla \cdot S_E \mathbb{T}^E + \mathbf{f}^E. \quad (54)$$

Equation (54) is a generalized version of the classical elastic dynamics. Its steady state is given by

$$\frac{1}{S_E} \nabla \cdot S_E \mathbb{T}^E + \mathbf{f}^E = 0. \quad (55)$$

Here, Eq. (55) describes the possible bending of the biomolecule due to the solvent-solute interaction potential force \mathbf{f}_{FSI}^E and the RF force \mathbf{f}_{RF}^E , which originates from non-uniform charge distributions. The bending and curvature of vesicle membranes due to protein interactions are popular research topics.^{52,119} However, most work in the literature is essentially qualitative. The Helfrich curvature and phase field models provide interesting phenomenological descriptions to relatively simple geometries.^{52,74,119} The proposed multiscale multiphysical models have a potential to provide new insights to the bending and curvature of macromolecular complexes.

In the present multiscale, multiphysics and multidomain theory, the generalized Laplace-Beltrami equation (35), Poisson equation (38), Nernst-Planck equation (42), Navier-Stokes equation (43), Newton's equations (46) and elastic equation (54) are directly or indirectly coupled to each other to form a system of governing equations for aqueous macromolecular complexes. Solution to these equations minimizes the total action functional and determines physical variables $\{S_I\}$, Φ , $\{\rho_\alpha\}$, \mathbf{v} , $\{\mathbf{z}_j\}$, and \mathbf{w} .

III Concluding remarks

Last decade has witnessed the continuous miniaturization of mechanical, chemical, thermal, optical, and electronic devices in the engineering sciences, meanwhile, an increased ability to manipulate large biomolecular complexes and subcellular organelles in biological sciences. These developments have led us to the exciting era of nanoscience and nanotechnology. However, nanoscale chemical, physical and biological systems pose fundamental challenges in theoretical modeling and numerical computation due to their excessively large number of degrees of freedom. Multiscale approaches are efficient strategies for dimensionality reduction of the aforementioned problems. The goal of multiscale analysis lies in developing new methodologies which sufficiently describe all the key physical observations, while dramatically reduce the total number of degrees of freedom so that the resulting systems are tackleable with the contemporary computer capability.

One of multiscale paradigms that is particularly suitable for the modeling and computation of aqueous chemical, physical and biological systems was introduced by the present author.¹⁶⁴ A major feature of this multiscale formalism is the use of differential geometry theory of surfaces as a versatile tool to geometrically divide the total computational domain into a macroscopic solvent domain and a microscopic solute domain, and dynamically coupling the continuum mechanics in the solvent domain and the discrete mechanics in the solute domain. An essential strategy of our approach is the use of energy functional to put multiphysics on an equal footing. Subsequently, key physical observables are served as the main variables of the energy functional and their variations give rise to coupled governing partial differential equations (PDEs). The solution of these PDEs results in the minimization of the energy functional. The incorporation of quantum descriptions further enhances the power of our multiscale formulation.^{21,23,33} Our multiscale paradigm has been extensively validated with experimental measurements, such as solvent free energies,^{31-34,149,176} binding affinities,³² current-voltage curves,^{21,23,166} etc. A limitation of our earlier theory is that only two domains, namely, a solvent domain and a solute domain, are employed. However, for large macromolecular complexes and sophisticated nano-bio devices, it is desirable to simultaneously invoke a number of differential physical descriptions for appropriate parts of the macromolecular complexes and/or nano-bio devices. The present work formulates such a multiscale, multiphysics and multidomain theory.

In the present formulation, the solvent domain is either represented with a dielectric continuum or equipped with fluid dynamics. A total of N different domains is assumed for macromolecular complexes. Depending on the need, these solute domains can be furnished with different physical descriptions, such as static atomistic point charges, molecular dynamics (MD), coarse grained dynamics, quantum mechanics, elasticity, etc. In all cases, the electrostatic interactions among all domains, which are delocalized and of long range, are carefully considered. Additionally, all the solvent-solute non-electrostatic interactions, including potential dipolar, multipole, dispersion and van der Waals interactions, are accounted. Moreover, ion-ion non-electrostatic interactions in the solvent domains are included. Appropriate force fields or interactions are assumed for MD, coarse-graining and quantum descriptions within their domains. To demonstrate these ideas, we have explicitly studied three multiscale, multiphysics and multidomain models. The first model is for solvation analysis. In this case, we consider a simple equilibrium system with dielectric continuum representation of the solvent and static charge density presentations of the solute complex, which is divided into multiple domains with different surface tensions, pressures, dielectric functions, and charge density distributions. The interactions among solvent components and between the solvent and the solute are accounted. Generalized Boltzmann distributions are used for ion densities. The morphology of each solute domain is governed by one generalized Laplace-Beltrami (LB) equation (i.e., geometric flow equation). Additionally, the multidomain Poisson-Boltzmann (PB) equation is obtained for the electrostatic potential. The second model is for charge transport in chemical, physical and biological systems. We formulate our theory for a non-equilibrium system whose generalized electrochemical potential does not vanish due to spatial inhomogeneities in densities and/or electrostatic potentials. For the dynamics of ion densities, the gradient flow approach is employed to construct a set of multidomain Nernst-Planck equations, which are

coupled to a multidomain Poisson equation for the electrostatic potential. These equations are further coupled with a total of N LB equations, one for each macromolecular domain. We have illustrated that this LB-PNP model recovers the LB-PB theory at equilibrium. Finally, we develop a fluid-electro-MD-elastic model. In this model, additional Navier-Stokes equations, Newton's equations, and elasticity equation are systematically derived for electrostatic fluid dynamics, molecular dynamics, and elastic dynamics, respectively. Force balances within or between domains are obtained via the total variation.

Although quantum mechanical treatment is not explicitly described in the present work, it is straightforward to add the quantum description in one or few domains. The related quantum formulation in the framework of our differential geometry based multiscale models has been developed in our earlier work.³³ For simplicity, we have omitted quantum description in the present work.

It is worthwhile to point out that our earlier quantum dynamics in continuum formalism^{21,23,24} is in fact a quantum density functional theory (qDFT). This method treats protons in the solvent quantum mechanically. The variation of its energy functionals results in a non-conventional Kohn-Sham equation for proton transport. Additionally, the LB-PNP model developed in our earlier work¹⁶⁶ and the present multidomain LB-PNP model are essentially non-convention density functional theory (DFT). Classical DFT of complex fluids^{68,170} has found its success in microstructure prediction. Unlike the classical DFT, which depends on hard-sphere approximations for correlations, our DFT utilizes realistic potentials. It will be interesting to compare the performance of our DFT methods with that of the classical DFT for real world problems. This aspect will be investigated in our future work.

The numerical validation of the present multiscale multiphysics and multidomain models is under our consideration. An interesting numerical issue is the verification that the proposed integral-differential LBPB model is capable of predicting solvent microstructures near the solvent-solute interfaces. Currently, more expensive integral equation theories, including hyper-netted chain equation, Carnahan-Starling equation, Percus-Yevick equation and density functional theory of liquids, are employed to deliver solvent microstructures at equilibrium.^{13,63,68,129,153}

The multidomain methodology proposed in the present work, in conjugation with our multiscale and multiphysics paradigm, is potentially useful in many chemical, physical and biological systems, including deoxyribonucleic acid (DNA) nanowires, molecular junctions, fuel cells, solar cells, battery cells, molecular switches, nanotubes, field effect transistors, nanofibers, thin films, ion channels, ATPases, neuron synapses, etc.

Acknowledgments

This work was supported in part by NSF grants CCF-0936830 and DMS-1160352, and NIH Grant R01GM-090208. The author acknowledges the Mathematical Biosciences Institute for hosting valuable workshops which lead to some of the present ideas.

Literature cited

1. Abraham FF, Broughton JQ, Bernstein N, Kaxiras E. Spanning the continuum to quantum length scales in a dynamic simulation of brittle fracture. *Europhys. Lett.* 1998; 44:783–787.
2. Allen R, Hansen J-P, Melchionna S. Electrostatic potential inside ionic solutions confined by dielectrics: a variational approach. *Phys Chem Chem Physics.* 2001; 3:4177–4186.
3. Baker, NA. Biomolecular applications of Poisson-Boltzmann methods.. In: Lipkowitz, KB.; Larter, R.; Cundari, TR., editors. *Reviews in Computational Chemistry.* Vol. 21. John Wiley and Sons; Hoboken, NJ: 2005.
4. Barcion V, Chen D, Eisenberg BS. Ion flow through narrow membrane channels: Part ii. *SIAM J. Appl. Math.* Oct.1992 52:1405–1425.
5. Bardhan JP, Eisenberg BS, Gillespie D. Discretization of the induced-charge boundary integral equation. *Physical Review E (Statistical, Nonlinear, and Soft Matter Physics).* 2009; 80(1):011906–10.
6. Barone V, Cossi M, Tomasi J. A new definition of cavities for the computation of solvation free energies by the polarizable continuum model. *Journal of Chemical Physics.* 1997; 107:3210–3221.
7. Bashford D, Case DA. Generalized Born models of macromolecular solvation effects. *Annual Review of Physical Chemistry.* 2000; 51:129–152.
8. Bates PW, Chen Z, Sun YH, Wei GW, Zhao S. Geometric and potential driving formation and evolution of biomolecular surfaces. *J. Math. Biol.* 2009; 59:193–231. [PubMed: 18941751]
9. Bates PW, Wei GW, Zhao S. The minimal molecular surface. arXiv:q-bio/0610038v1. 2006 [q-bio.BM].
10. Bates PW, Wei GW, Zhao S. Minimal molecular surfaces and their applications. *Journal of Computational Chemistry.* 2008; 29(3):380–91. [PubMed: 17591718]
11. Bazant MZ, Kilic MS, Storey BD, Ajdari A. Towards an understanding of induced-charge electrokinetics at large applied voltages in concentrated solutions. *Advances in Colloid and Interface Science.* 2009; 152:48–88. [PubMed: 19879552]
12. Beglov D, Roux B. Solvation of complex molecules in a polar liquid: an integral equation theory. *Journal of Chemical Physics.* 1996; 104(21):8678–8689.
13. Beglov D, Roux B. An integral equation to describe the solvation of polar molecules in liquid water. *J. Phys. Chem. B.* 1997; 101:7821–7826.
14. Belgrader P, Okuzumi M, Pourahmadi F, Borkholder DA, Northrup MA. A microfluidic cartridge to prepare spores for pcr analysis. *Biosensors Bioelectronics.* 2000; 14:849–852. [PubMed: 10945459]
15. Borukhov I, Andelman D. Steric effects in electrolytes: A modified poisson-boltzmann equation. *Phys. Rev. Lett.* 1997; 79(3):435–438.
16. Bufler FM, Schenk A, Fichtner W. Efficient monte carlo device modeling. *IEEE T Electron Devices.* 2000; 47:1891–1897.
17. Burger M, Schlake B, Wolfram MT. Nonlinear poisson-nernst-planck equations for ion flux through confined geometries. *Nonlinearity.* 2012; 25:961–990.
18. Cancès E, Mennucci B, Tomasi J. A new integral equation formalism for the polarizable continuum model: Theoretical background and applications to isotropic and anisotropic dielectrics. *Journal of Chemical Physics.* 1997; 107:3032–3041.
19. Cardenas AE, Coalson RD, Kurnikova MG. Three-dimensional Poisson-Nernst-Planck theory studies: Influence of membrane electrostatics on Gramicidin A channel conductance. *Biophysical Journal.* Jul.2000 79:80–93. [PubMed: 10866939]
20. Chandler D. Derivation of an integral equation for pair correlation functions in molecular fluids. *J. Chem. Phys.* 1973; 59:2742–2746.
21. Chen D, Chen Z, Wei GW. Quantum dynamics in continuum for proton transport II: Variational solvent-solute interface. *International Journal for Numerical Methods in Biomedical Engineering.* 2012; 28:25–51. [PubMed: 22328970]
22. Chen D, Wei GW. Modeling and simulation of electronic structure, material interface and random doping in nano-electronic devices. *J. Comput. Phys.* 2010; 229:4431–4460. [PubMed: 20396650]

23. Chen D, Wei GW. Quantum dynamics in continuum for proton transport—Generalized correlation. *J Chem. Phys.* 2012; 136:134109. [PubMed: 22482542]
24. Chen D, Wei GW. Quantum dynamics in continuum for proton transport I: Basic formulation. *Commun. Comput. Phys.* 2013; 13:285–324. [PubMed: 23550030]
25. Chen D, Wei GW, Cong X, Wang G. Computational methods for optical molecular imaging. *Communications in Numerical Methods in Engineering.* 2009; 25:1137–1161. [PubMed: 20485461]
26. Chen DP, Eisenberg RS, Jerome JW, Shu CW. Hydrodynamic model of temperature change in open ionic channels. *Biophys. J.* 1995; 69:2304–2322. [PubMed: 8599638]
27. Chen HN, Wu YJ, Voth GA. Proton transport behavior through the influenza A M2 channel: Insights from molecular simulation. *Biophys J.* 2007; 93:3470–3479. [PubMed: 17693473]
28. Chen JL, Noodleman L, Case DA, Bashford D. Incorporating solvation effects into density-functional electronic-structure calculations. *J. Phys. Chem.* 1994; 98:11059–11068.
29. Chen L, Conlisk AT. Electroosmotic flow and particle transport in micro/nano nozzles and diffusers. *Biomedical Microdevices.* 2008; 10:289–289. [PubMed: 18034305]
30. Chen QB, Liu ZF, Wong CH. An ab initio molecular dynamics study on the solvation of formate ion and formic acid in water. *Journal of Theoretical and Computational Chemistry.* 2012; 11:1019–1032.
31. Chen Z, Baker NA, Wei GW. Differential geometry based solvation models I: Eulerian formulation. *J. Comput. Phys.* 2010; 229:8231–8258. [PubMed: 20938489]
32. Chen Z, Baker NA, Wei GW. Differential geometry based solvation models II: Lagrangian formulation. *J. Math. Biol.* 2011; 63:1139–1200. [PubMed: 21279359]
33. Chen Z, Wei GW. Differential geometry based solvation models III: Quantum formulation. *J. Chem. Phys.* 2011; 135(194108)
34. Chen Z, Zhao S, Chun J, Thomas DG, Baker NA, Bates PB, Wei GW. Variational approach for nonpolar solvation analysis. *Journal of Chemical Physics.* 137(084101):2012.
35. Cheng MH, Coalson RD. An accurate and efficient empirical approach for calculating the dielectric self-energy and ion-ion pair potential in continuum models of biological ion channels. *J Phys Chem B.* 2005; 109(1):488–98. [PubMed: 16851040]
36. Cheng MH, Coalson RD, Tang P. Molecular dynamics and brownian dynamics investigation of ion permeation and anesthetic halothane effects on a proton-gated ion channel. *J Am Chem Soc.* 2010; 132(46):16442–9. [PubMed: 20979415]
37. Cheng Y, Gamba IM, Majorana A, Shu C-W. A discontinuous galerkin solver for boltzmannpoisson systems in nano devices. *Computer Methods in Applied Mechanics and Engineering.* 2009; 198:3130–3150.
38. Chiba M, Fedorov DG, Kitaura K. Polarizable continuum model with the fragment molecular orbital-based time-dependent density functional theory. *Journal of Computational Chemistry.* 2008; 29:2667–2676. [PubMed: 18484637]
39. Chou T. Enhancement of charged macromolecule capture by nanopores in a salt gradient. *J. Chem. Phys.* 2009; 131(034703)
40. Choudhary OP, Ujwal R, Kowallis W, Coalson R, Abramson J, Grabe M. The electrostatics of VDAC: implications for selectivity and gating. *J Mol Biol.* 2010; 396(3):580–92. [PubMed: 20005234]
41. Chung S-H, Kuyucak S. Recent advances in ion channel research. *Biochimica et Biophysica Acta.* 2002; 1565:267–286. [PubMed: 12409200]
42. Coalson RD, Kurnikova MG. Poisson-Nernst-Planck theory approach to the calculation of current through biological ion channels. *IEEE Trans Nanobioscience.* 2005; 4(1):81–93. [PubMed: 15816174]
43. Connolly ML. Depth buffer algorithms for molecular modeling. *J. Mol. Graphics.* 1985; 3:19–24.
44. Corry B, Kuyucak S, Chung S-H. Dielectric self-energy in Poisson-Boltzmann and Poisson-Nernst-Planck models of ion channels. *Biophysical Journal.* 2003; 84(6):3594–3606. [PubMed: 12770869]

45. Cossi M, Barone V, Cammi R, Tomasi J. Ab initio study of solvated molecules: A new implementation of the polarizable continuum model. *Chemical Physics Letters*. 1996; 255:327–335.
46. Cui Q. Combining implicit solvation models with hybrid quantum mechanical/molecular mechanical methods: A critical test with glycine. *Journal of Chemical Physics*. 2002; 117(10): 4720.
47. Datta S. Nanoscale device modeling: the Green's function method. *Superlattices and Microstructures*. 2000; 28:253–278.
48. Datta, S. *Electronic Transport in Mesoscopic Systems*. Cambridge University Press; 1995.
49. Davis ME, McCammon JA. Electrostatics in biomolecular structure and dynamics. *Chemical Reviews*. 1990; 94:509–21.
50. Diehla A, Tamashirob MN, Barbosac MC, Levinc Y. Density-functional theory for attraction between like-charged plates. *Physica A: Statistical Mechanics and its Applications*. 1999; 274:433445.
51. Dominy BN, Brooks CL III. Development of a generalized Born model parameterization for proteins and nucleic acids. *Journal of Physical Chemistry B*. 1999; 103(18):3765–3773.
52. Du Q, Liu C, Wang XQ. A phase field approach in the numerical study of the elastic bending energy for vesicle membranes. *J. Comput. Phys*. 2004; 198:450–468.
53. Duffy DC, Gillis HL, Lin J, Sheppard NF, Kellogg GJ. Microfabricated centrifugal microfluidic systems: Characterization and multiple enzymatic assay. *Analytical Chemistry*. 1999; 71:5206–5212.
54. Duncan A, Sedgewick RD, Coalson RD. Improved local lattice approach for Coulombic simulations. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2005; 71:046702. [PubMed: 15903813]
55. Dzubiella J, Swanson JMJ, McCammon JA. Coupling hydrophobicity, dispersion, and electrostatics in continuum solvent models. *Physical Review Letters*. 2006; 96:087802. [PubMed: 16606226]
56. W. N. E, Engquist B, Li X, Ren W, Vanden-Eijnden E. Heterogeneous multiscale methods: A review. *Commun. Comput. Phys*. 2007; 2:367–450.
57. Eisenberg BS, Chen D. Poisson-Nernst-Planck (PNP) theory of an open ionic channel. *Biophysical Journal*. 1993; 64:A22.
58. Eisenberg BS, Hyon YK, Liu C. Energy variational analysis of ions in water and channels: Field theory for primitive models of complex ionic fluids. *Journal of Chemical Physics*. 2010; 133:104104. [PubMed: 20849161]
59. Federer H. Curvature Measures. *Trans. Amer. Math. Soc*. 1959; 93:418–491.
60. Fischetti MV. Master-equation approach to the study of electronic transport in small semiconductor devices. *Phys. Rev. B*. 1999; 59:4901–4917.
61. Fogolari F, Briggs JM. On the variational approach to Poisson-Boltzmann free energies. *Chemical Physics Letters*. 1997; 281:135–139.
62. Fogolari F, Brigo A, Molinari H. The Poisson-Boltzmann equation for biomolecular electro-statics: a tool for structural biology. *Journal of Molecular Recognition*. 2002; 15(6):377–92. [PubMed: 12501158]
63. Fries PH, Patey GN. The solution of the hypernetted-chain approximation for fluids of nonspherical particles. a general method with application to dipolar hard spheres. *Journal of Chemical Physics*. 1985; 82:429–440.
64. Frydel D. Polarizable poisson-boltzmann equation: The study of polarizability effects on the structure of a double layer. *J. Chem. Phys*. 2011; 134:234704. [PubMed: 21702573]
65. Fu Z, Li X, Merz J, K. M. Accurate assessment of the strain energy in a protein-bound drug using QM/MM x-ray refinement and converged quantum chemistry. *J. Comput. Chem*. 2011; 32:2587–259. [PubMed: 21598285]
66. Gallicchio E, Zhang LY, Levy RM. The SGB/NP hydration free energy model based on the surface generalized Born solvent reaction field and novel nonpolar hydration free energy estimators. *Journal of Computational Chemistry*. 2002; 23(5):517–29. [PubMed: 11948578]

67. Geng W, Wei GW. Multiscale molecular dynamics using the matched interface and boundary method. *J Comput. Phys.* 2011; 230(2):435–457. [PubMed: 21088761]
68. Gillespie D, Nonner W, Eisenberg BS. Coupling poisson-nernst-planck and density functional theory to calculate ion flux. *Journal of Physics: Condensed Matter.* 2002; 14(46):12129–12145.
69. Gilson MK, Davis ME, Luty BA, McCammon JA. Computation of electrostatic forces on solvated molecules using the Poisson-Boltzmann equation. *Journal of Physical Chemistry.* 1993; 97(14): 3591–3600.
70. Grant JA, Pickup BT, Sykes MT, Kitchen CA, Nicholls A. The Gaussian Generalized Born model: application to small molecules. *Physical Chemistry Chemical Physics.* 2007; 9:4913–22. [PubMed: 17912422]
71. Grochowski P, Trylska J. Continuum molecular electrostatics, salt effects, and counterion binding: a review of the poisson-boltzmann theory and its modifications. *Biopolymers.* 2008; 89(2):93–113. [PubMed: 17969016]
72. Hadd AG, Jacobson SC, Ramsey JM. Microfluidic assays of acetylcholinesterase inhibitors. *Analytical Chemistry.* 1999; 71:5206–5212.
73. Han ZY, Goldsman N, Lin CK. Incorporation of quantum corrections to semiclassical two-dimensional device modeling with the Wigner-Boltzmann equation. *Solid-State Electronics.* 2005; 49:145–154.
74. Helfrich W. Elastic properties of lipid bilayers: Theory and possible experiments. *Zeitschrift für Naturforschung Teil C.* 1973; 28:693–703.
75. Holm, C.; Kekicheff, P.; Podgornik, R. *Electrostatic effects in soft matter and biophysics*; NATO Science Series. Kluwer Academic Publishers; Boston: 2001.
76. Honig B, Nicholls A. Classical electrostatics in biology and chemistry. *Science.* 1995; 268(5214): 1144–9. [PubMed: 7761829]
77. Hori T, Takahashi H, Nakano M, Nitta T, Yang W. A qm/mm study combined with the theory of energy representation: Solvation free energies for anti/syn acetic acids in aqueous solution. *Chemical Physics Letters.* 2006; 419(1-3):240–244.
78. Hou GH, Zhu X, Elstner M, Cui Q. A modified qm/mm hamiltonian with the self-consistent-charge density-functional-tight-binding theory for highly charged qm regions. *J. Chem. Theory and Comput.* 2012; 8:4293–4304. [PubMed: 23275762]
79. Hu LH, Wei GW. Nonlinear poisson equation for heterogeneous media. *Biophysical Journal.* 2012:758–766. [PubMed: 22947937]
80. Hyon Y, Eisenberg BS, Liu C. A mathematical model for the hard sphere repulsion in ionic solution. *Commun. Math. Sci.* 2011; 9:459–475.
81. Im W, Beglov D, Roux B. Continuum solvation model: electrostatic forces from numerical solutions to the Poisson-Boltzmann equation. *Computer Physics Communications.* 1998; 111(1-3): 59–75.
82. Improta R, Barone V, Scalmani G, Frisch MJ. A state-specific polarizable continuum model time dependent density functional theory method for excited state calculations in solution. *Journal of Chemical Physics.* 2006; 125(054103)
83. Ishikuro H, Hiramoto T. Hopping transport in multiple-dot silicon single electron mosfet. *Solid-State Electronics.* 1998; 42:1425–1428.
84. Jacoboni, C.; Lugli, P. *The Monte Carlo Method for Semiconductor Device Simulation*. Springer-Verlag; New York: 1989.
85. Jinnouchi R, Anderson AB. Electronic structure calculations of liquid-solid interfaces: Combination of density functional theory and modified Poisson-Boltzmann theory. *PHYSICAL REVIEW B.* 2008; 77(245417)
86. Jung YW, Lu BZ, Mascagni M. A computational study of ion conductance in the KcsA K⁺ channel using a Nernst-Planck model with explicit resident ions. *J. Chem. Phys.* 2009; 131(215101)
87. Kadanoff L, Byam G. *Quantum Statistical Mechanics.* 1962
88. Kamholz AE, Weigl BH, Finlayson BA, Yager P. Quantitative analysis of molecular interaction in a microfluidic channel: The t-sensor. *Analytical Chemistry.* 1999; 71:5340–5347. [PubMed: 10596213]

89. Kanduc M, Naji MA, Jho YS, Pincus PA, Podgornik R. The role of multipoles in counterion-mediated interactions between charged surfaces: strong and weak coupling. *Journal of Physics: Condensed Matter*. 2009; 21:424103.
90. Kilic MS, Bazant MZ, Ajdari A. Steric effects in the dynamics of electrolytes at large applied voltages. II. modified poisson-nernst-planck equations. *Phys. Rev. E*. 2007; 75(021503):16.
91. Kim BY, Yang J, Gong MJ, Flachsbarth BR, Shannon MA, Bohn PW, Sweedler JV. Multidimensional separation of chiral amino acid mixtures in a multilayered three-dimensional hybrid microfluidic/nanofluidic device. *J. Anal. Chem.* 2009; 81:2715–2722.
92. Kim J. Phase-field models for multi-component fluid flows. *Commun. Comput. Phys.* 2012; 12:613–661.
93. Kirmizialtin S, Pabit SA, Meisburger SP, Pollack L, Elber R. RNA and its ionic cloud: Solution scattering experiments and atomically detailed simulations. *Biophysical J.* 2012; 102:819–828.
94. Kiselev YV, Leda M, Lobanov AI, Marenduzzo D, Goryachev AB. Lateral dynamics of charged lipids and peripheral proteins in spatially heterogeneous membranes: Comparison of continuous and monte carlo approaches. *J. Chem. Phys.* 2011; 135(155103)
95. Knap J, Ortiz M. Spanning the continuum to quantum length scales in a dynamic simulation of brittle fracture. *J. Mech. Phys. Solids*. 2001; 49:1899–1923.
96. Knepley M, Karpeev DA, Davidovits S, Eisenberg RS, Gillespie D. An efficient algorithm for classical density functional theory in three dimensions: Ionic solutions. *J. Chem. Phys.* 2010; 132:124101. [PubMed: 20370108]
97. Koehl P. Electrostatics calculations: latest methodological advances. *Current Opinion in Structural Biology*. 2006; 16(2):142–51. [PubMed: 16540310]
98. Kurnikova MG, Coalson RD, Graf P, Nitzan A. A lattice relaxation algorithm for Three-Dimensional Poisson-Nernst-Planck theory with application to ion transport through the Gramicidin A channel. *Biophysical Journal*. 1999; 76:642–656. [PubMed: 9929470]
99. Kuyucak S, Andersen OS, Chung S-H. Models of permeation in ion channels. *Rep. Prog. Phys.* 2001; 64:1427–1472.
100. Lake R, Klimeck G, Bowen RC, Jovanovic D. Single and multiband modeling of quantum electron transport through layered semiconductor devices. *Journal of Applied Physics*. 1997; 81:7845–7869.
101. Lamm, G. The Poisson-Boltzmann equation.. In: Lipkowitz, KB.; Larter, R.; Cundari, TR., editors. *Reviews in Computational Chemistry*. John Wiley and Sons, Inc.; Hoboken, N.J.: 2003. p. 147-366.
102. Larini L, Lu L, Voth GA. The multiscale coarse-graining method. vi. implementation of three-body coarse-grained potentials. *JOURNAL OF CHEMICAL PHYSICS*. 2010; 132(164107)
103. Levin Y. Electrostatic correlations: from plasma to biology. *Rep. Prog. Phys.* 2002; 65:1577–1632.
104. Levitt DG. Interpretation of biological ion channel flux data—reaction-rate versus continuum theory. *Annual Review of Biophysics and Biophysical Chemistry*. 1986; 15:29–57.
105. Levitt DG. Modeling of ion channels. *J. Gen. Physiol.* 1999; 113(6):789–794. [PubMed: 10352030]
106. Li B, Lu BZ, Wang ZM, McCammon JA. Solutions to a reduced Poisson-Nernst-Planck system and determination of reaction rates. *Physica A*. 2010; 389(7):1329–1345. [PubMed: 20228879]
107. Li L, Ismagilov RF. Protein crystallization using microfluidic technologies based on valves, droplets, and slipchip. *Annual Review of Biophysics*. 2010; 39
108. Lu Q, Luo R. A Poisson-Boltzmann dynamics method with nonperiodic boundary condition. *Journal of Chemical Physics*. 2003; 119(21):11035–11047.
109. Macounova K, Cabrera CR, Holl MR, Yager P. Generation of natural pH gradients in microfluidic channels for use in isoelectric focusing. *Analytical Chemistry*. 2000; 72:3745–3751. [PubMed: 10959958]
110. Mamonov AB, Coalson RD, Nitzan A, Kurnikova MG. The role of the dielectric barrier in narrow biological channels: A novel composite approach to modeling single-channel currents. *Biophysical Journal*. Jun.2003 84:3646–3661. [PubMed: 12770873]

111. Mamonov AB, Kurnikova MG, Coalson RD. Diffusion constant of K⁺ inside Gramicidin A: a comparative study of four computational methods. *Biophys Chem.* 2006; 124:268–78. [PubMed: 16797116]
112. Manciu M, Ruckenstein E. On the chemical free energy of the electrical double layer. *Langmuir.* 2003; 19(4):1114–1120.
113. Mei Y, Ji CG, Zhang JZH. A new quantum method for electrostatic solvation energy of protein. *J. Chem. Phys.* 2006; 125(094906)
114. Mongan J, Simmerling C, McCammon JA, Case DA, Onufriev A. Generalized Born model with a simple, robust molecular volume correction. *Journal of Chemical Theory and Computation.* 2007; 3(1):159–69.
115. Mukhopadhyay A, Fenley AT, Tolokh IS, Onufriev AV. Charge hydration asymmetry: The basic principle and how to use it to test and improve water models. *J. Phys. Chem. B.* 2012; 116:9776–9783. [PubMed: 22762271]
116. Nagle JF, Morowitz HJ. Molecular mechanisms for proton transport in membranes. *Proc. Natl. Acad. Sci. U.S.A.* 1978; 1458(72):298–302. [PubMed: 272644]
117. Netz RR, Orland H. Beyond Poisson-Boltzmann: Fluctuation effects and correlation functions. *European Physical Journal E.* 2000; 1(2-3):203–14.
118. Onufriev A, Case DA, Bashford D. Effective Born radii in the generalized Born approximation: the importance of being perfect. *Journal of Computational Chemistry.* 2002; 23(14):1297–304. [PubMed: 12214312]
119. Ou-Yang ZC, Helfrich W. Bending energy of vesicle membranes: General expressions for the first, second, and third variation of the shape energy and applications to spheres and cylinders. *Phys. Rev. A.* 1989; 39:5280–5288. [PubMed: 9901091]
120. Patra CN, Yethiraj A. Density functional theory for the distribution of small ions around polyions. *J. Phys. Chem. B.* 1999; 101:6080–6087.
121. Pattanayak SK, Chowdhuri S. Size dependence of solvation structure and dynamics of ions in liquid n-methylacetamide: A molecular dynamics simulation study. *Journal of Theoretical and Computational Chemistry.* 2012; 11:361–377.
122. Peskin CS. Numerical analysis of blood flow in the heart. *J. Comput. Phys.* 1977; 25(3):220–52.
123. Pettitt BM, R. P. R. Integral equation predictions of liquid state structure for waterlike intermolecular potentials. *J. Chem. Phys.* 1982; 77:1451–1457.
124. Pierotti RA. A scaled particle theory of aqueous and nonaqueous solutions. *Chemical Reviews.* 1976; 76(6):717–726.
125. Pomes R, Roux B. Structure and Dynamics of a Proton Wire: A Theoretical Study of H⁺ Translocation along the Single-File Water Chain in the Gramicidin A Channel. *Biophysical Journal.* 2002; 71:19–39. [PubMed: 8804586]
126. Rice CL, Whitehead R. Electrokinetic flow in a narrow cylindrical capillary. *Journal of Physical Chemistry.* 1965; 69:4017–4024.
127. Rocchia W, Alexov E, Honig B. Extending the applicability of the nonlinear poisson-boltzmann equation: Multiple dielectric constants and multivalent ions. *J. Phys. Chem.* 2001; 105:6507–6514.
128. Rosenfeld Y. Free energy model for inhomogeneous fluid mixtures: Yukawa charged hard spheres, general interactions, and plasmas. *J. Chem. Phys.* 1993; 98:8126–8148.
129. Roth R. Fundamental measure theory for hard-sphere mixtures: a review. *J. Phys.: Condens. Matter.* 2010; 22:063102. [PubMed: 21389360]
130. Roux B, Allen T, Berneche S, Im W. Theoretical and computational models of biological ionchannels. *Quarterly Reviews of Biophysics.* 2004; 7(1):1–103.
131. Roux B, Simonson T. Implicit solvent models. *Biophysical Chemistry.* 1999; 78(1-2):1–20. [PubMed: 17030302]
132. Sanner MF, Olson AJ, Spehner JC. Reduced surface: An efficient way to compute molecular surfaces. *Biopolymers.* 1996; 38:305–320. [PubMed: 8906967]

133. Schneck E, Sedlmeier F, Netz RR. Hydration repulsion between biomembranes results from an interplay of dehydration and depolarization. *PNAS*. 2012; 109:14405–14409. [PubMed: 22908241]
134. Schnieders MJ, Baker NA, Ren P, Ponder JW. Polarizable atomic multipole solutes in a Poisson-Boltzmann continuum. *Journal of Chemical Physics*. 2007; 126:124114. [PubMed: 17411115]
135. Schuss Z, Nadler B, Eisenberg BS. Derivation of Poisson and Nernst-Planck equations in a bath and channel from a molecular model. *Phys. Rev. E Stat Nonlin Soft Matter Phys*. 2001; 64:036116. [PubMed: 11580403]
136. Schwinger J. Brownian motion of a quantum oscillator. *J. Math. Phys*. 1961; 2:407–432.
137. Sharp KA, Honig B. Calculating total electrostatic energies with the nonlinear Poisson-Boltzmann equation. *Journal of Physical Chemistry*. 1990; 94:7684–7692.
138. Sharp KA, Honig B. Electrostatic interactions in macromolecules - theory and applications. *Annual Review of Biophysics and Biophysical Chemistry*. 1990; 19:301–332.
139. Simakov NA, Kurnikova MG. Soft wall ion channel in continuum representation with application to modeling ion currents in α -hemolysin. *J. Phys. Chem. B*. 2010; 114(46):15180C15190. [PubMed: 21028776]
140. Singer A, Gillespie D, Norbury J, Eisenberg RS. Singular perturbation analysis of the steady state Poisson-Nernst-Planck system: Applications to ion channels. *European Journal of Applied Mathematics*. 2008; 19:541–560. [PubMed: 19809600]
141. Snider RF. Quantum-mechanical modified boltzmann equation for degenerate internal states. *J. Chem. Phys*. 1960; 32:1051–1060.
142. Snider RF, Wei GW, Muga JG. Moderately dense gas quantum kinetic theory: Aspects of pair correlations. *J. Chem. Phys*. 1996; 105:3057–3065.
143. Snider RF, Wei GW, Muga JG. Moderately dense gas quantum kinetic theory: Transport coefficient expressions. *J. Chem. Phys*. 1996; 105:3066–3078.
144. Stillinger FH. Structure in aqueous solutions of nonpolar solutes from the standpoint of scaled-particle theory. *J. Solution Chem*. 1973; 2:141–158.
145. Svizhenko A, Anantram M, Govindan TR, Biegel B, Venugopal R. Two-dimensional quantum mechanical modeling of nanotransistors. *J Applied Phys*. 2002; 91:2343–2354.
146. Tadmor EB, Ortiz M, Phillips R. Quasicontinuum analysis of defects in crystals. *Phil. Mag. A*. 1996; 76:1529–1564.
147. Takano Y, Houk KN. Benchmarking the conductor-like polarizable continuum model (cpcm) for aqueous solvation free energies of neutral and ionic organic molecules. *Journal of Chemical Theory and Computation*. 2005; 1(1):70–77.
148. Tang S, Hou TY, Liu WK. A pseudo-spectral multiscale method: interfacial conditions and coarse grid equations. *J. Comput. Phys*. 2006; 213:57–85.
149. Thomas D, Chun J, Chen Z, Wei GW, Baker NA. Parameterization of a geometric flow implicit solvation model. *J. Comput. Chem*. 2013
150. Tjong H, Zhou HX. GBr6NL: A generalized Born method for accurately reproducing solvation energy of the nonlinear Poisson-Boltzmann equation. *Journal of Chemical Physics*. 2007; 126:195102. [PubMed: 17523838]
151. Tomasi J, Mennucci B, Cammi R. Quantum mechanical continuum solvation models. *Chem. Rev*. 2005; 105:2999–3093. [PubMed: 16092826]
152. Tsui V, Case DA. Molecular dynamics simulations of nucleic acids with a generalized Born solvation model. *Journal of the American Chemical Society*. 2000; 122(11):2489–2498.
153. Tully-Smith DM, Reiss H. Further development of scaled particle theory of rigid sphere fluids. *Journal of Chemical Physics*. 1970; 53(10):4015–25.
154. Tyagi S, Suzen M, Sega M, Barbosa M, Kantorovich SS, Holm C. An iterative, fast, linear-scaling method for computing induced charges on arbitrary dielectric boundaries. *J Chem Phys*. 2010; 132(15):154112–9. [PubMed: 20423173]
155. Vlachy V. Ionic effects beyond poisson-boltzmann theory. *Annu. Rev. Phys. Chem*. 1999; 50:145–165. [PubMed: 15012409]

156. Wagoner JA, Baker NA. Assessing implicit models for nonpolar mean solvation forces: the importance of dispersion and volume terms. *Proceedings of the National Academy of Sciences of the United States of America*. 2006; 103(22):8331–6. [PubMed: 16709675]
157. Waisman E, Lebowitz JL. Mean spherical model integral equation for charged hard spheres I. method of solution. *J. Chem. Phys.* 1972; 56:3086–3093.
158. Waldmann L. Die Boltzmann-Gleichung für Gase mit rotierenden Molekülen. *Z. Naturforsch. Teil A*. 1957; 12:660–662.
159. Wang J, Lin M, Crenshaw A, Hutchinson A, Hicks B, Yeager M, Berndt S, Huang WY, Hayes RB, Chanock SJ, Jones RC, Ramakrishnan R. High-throughput single nucleotide polymorphism genotyping using nanofluidic dynamic arrays. *BMC Genomics*. 2009; 10(561)
160. Wang J, Zhu W, Li GH, Hansmann UHE. Velocity-scaling optimized replica exchange molecular dynamics of proteins in a hybrid explicit /implicit solvent. *J. Chem. Phys.* 2011; 135:084115. [PubMed: 21895167]
161. Wang K, Yu Y-X, Gao d G.-H. Density functional study on the structures and thermodynamic properties of small ions around polyanionic dna. *Phys. Rev. E*. 2004; 70:011912.
162. Wang W, Shu CW. The wkb local discontinuous galerkin method for the simulation of schrodinger equation in a resonant tunneling diode. *Journal of Scientific Computing*. 2009; 40:360–374.
163. Wei GW. Generalized Perona-Malik equation for image restoration. *IEEE Signal Processing Lett.* 1999; 6:165–167.
164. Wei GW. Differential geometry based multiscale models. *Bulletin of Mathematical Biology*. 2010; 72:1562–1622. [PubMed: 20169418]
165. Wei GW, Sun YH, Zhou YC, Feig M. Molecular multiresolution surfaces. *arXiv:math-ph/0511001v1*. 2005:1–11.
166. Wei G-W, Zheng Q, Chen Z, Xia K. Variational multiscale models for charge transport. *SIAM Review*. 2012; 54(4):699–754. [PubMed: 23172978]
167. Weigl BH, Yager P. Silicon-microfabricated diffusion-based optical chemical sensor. *Sensors and Actuators B-Chemical*. 1997; 39:452–457.
168. Wu DP, Steckl AJ. High speed nanofluidic protein accumulator. *Lab on a Chip*. 2009; 9:1890–1896. [PubMed: 19532964]
169. Wu J, Xia Z, Shen HJ, Li GH, Ren PY. Gay-berne and electrostatic multipole based coarse grained model and application with polyalanine in implicit solvent. *J. Chem. Phys.* 2011; 135:155104. [PubMed: 22029338]
170. Wu JZ, Li ZD. Density-functional theory for complex fluids. *Annu. Rev. Phys. Chem.* 2007; 58:85–112. [PubMed: 17052165]
171. Xie D, Jiang Y, Brune P, Scott LR. A fast solver for a nonlocal dielectric continuum model. *SIAM Journal on Scientific Computing*. 2012; 34:B107–B126.
172. Yoo J, Aksimentiev A. Competitive binding of cations to duplex dna revealed through molecular dynamics simulations. *J. Phys. Chem. B*. 2005; 116:12946–12954. [PubMed: 23016894]
173. Yu YX, Wu JZ, Gao GH. Density-functional theory of spherical electric double layers and ζ potentials of colloidal particles in restricted-primitive-model electrolyte solutions. *J. Chem. Phys.* 2004; 120:7223–7233. [PubMed: 15267630]
174. Zerah G, Hansen JP. Self-consistent integral equations for fluid pair distribution functions: Another attempt. *J. Chem. Phys.* 1984; 84:2336–2043.
175. Zhang Y, Bajaj C, Xu G. Surface smoothing and quality improvement of quadrilateral/hexahedral meshes with geometric flow. *Communications in Numerical Methods in Engineering*. 2009; 25:1–18. [PubMed: 19829757]
176. Zhao S. Pseudo-time-coupled nonlinear models for biomolecular surface representation and solvation analysis. *International Journal for Numerical Methods in Biomedical Engineering*. 2011; 27:1964–1981.
177. Zheng Q, Chen D, Wei GW. Second-order Poisson-Nernst-Planck solver for ion transport. *Journal of Comput. Phys.* 2011; 230:5239–5262.

178. Zheng Q, Wei GW. Poisson-Boltzmann-Nernst-Planck model. *Journal of Chemical Physics*. 2011; 134:194101. [PubMed: 21599038]
179. Zheng Q, Yang SY, Wei GW. Molecular surface generation using PDE transform. *International Journal for Numerical Methods in Biomedical Engineering*. 2012; 28:291–316. [PubMed: 22582140]
180. Zheng Z, Hansford DJ, Conlisk AT. Effect of multivalent ions on electroosmotic flow in micro- and nanochannels. *Electrophoresis*. 2003; 24:3006–3017. [PubMed: 12973804]
181. Zhou YC, Holst MJ, McCammon JA. A nonlinear elasticity model of macromolecular conformational change induced by electrostatic forces. *Journal of Mathematical Analysis and Applications*. 2008; 340:135–164. [PubMed: 19461946]
182. Zhu J, Alexov E, Honig B. Comparative study of generalized Born models: Born radii and peptide folding. *Journal of Physical Chemistry B*. 2005; 109(7):3008–22.

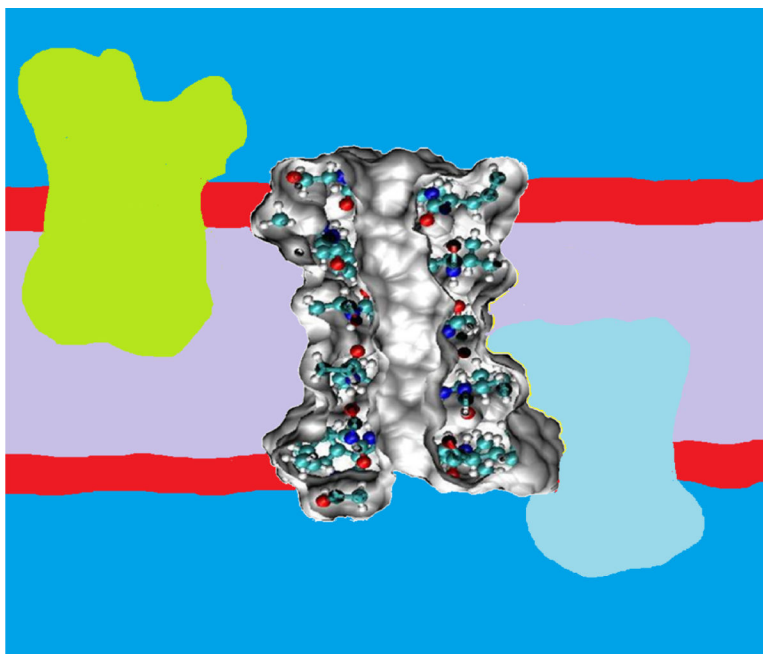


Figure 1. Illustration of multiscale, multiphysics and multidomain models with a protein-membrane complex. Multiphysical descriptions at multiscales are employed in multidomains, which are labeled with different colors.